The Development of Oral Arsenic Trioxide for Cancer Treatment: Academic Success, Economic Implications and Global Perspectives

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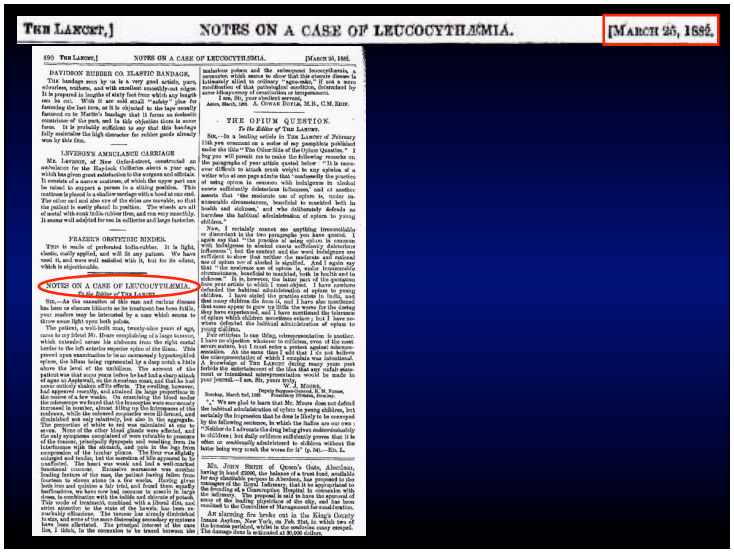
Queen Mary Hospital
Hong Kong

Arsenic

Medicinal use of arsenic has been known for centuries in China and medieval Europe

Description of Arsenic trioxide in Compendium of Materia Medica (Li ShiZhen) In the Ming Dynasty

砒石：又名信石，李時珍本草綱目中指砒石能治〝風痰在胸膈，可作吐藥。不可久服，傷人〞。



THE LANCET,] NOTES ON A CASE OF LEUCOCYTHÆMIA. [MARCH 26, 1892.

190 THE LANCET,] NOTES ON A CASE OF LEUCOCYTHÆMIA. [MARCH 26, 1892.

DAVIDSON RUBBER CO. ELASTIC BANDAGE.

LIVESON'S AMBULANCE CARRIAGE

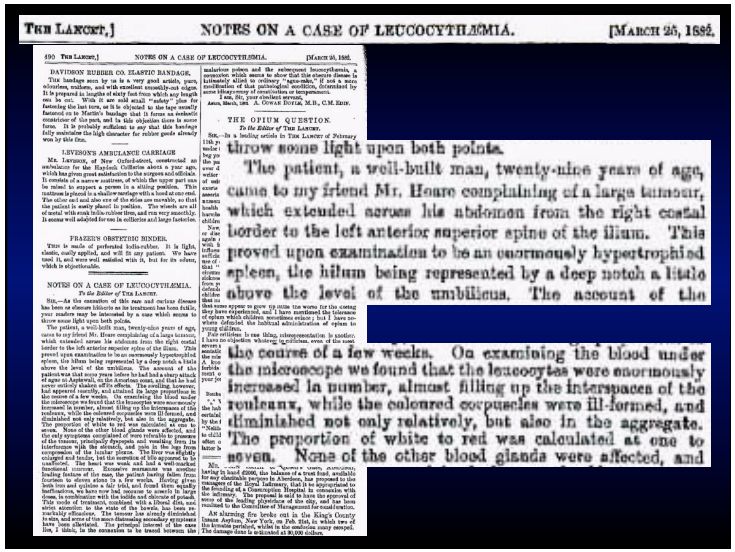
FRAZER'S OBSTETRIC BINDER.

NOTES ON A CASE OF LEUCOCYTHÆMIA

To the Editor of THE LANCET.

THE OPIUM QUESTION.

To the Editor of THE LANCET.

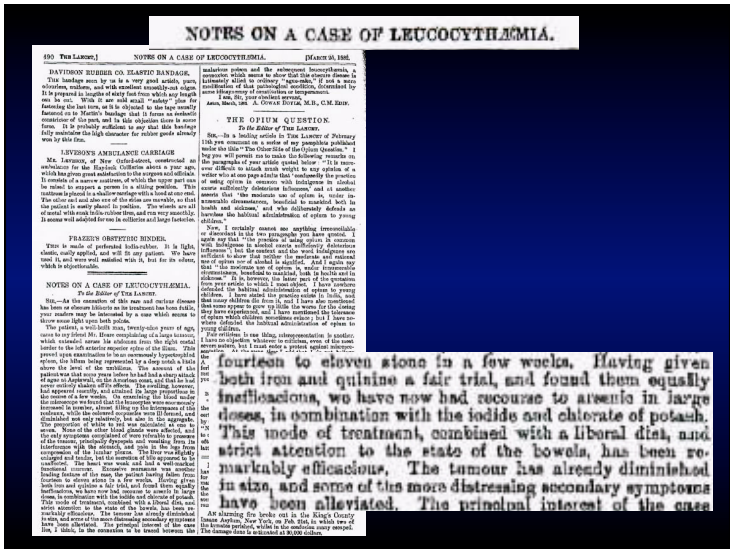

THE LANCET,] NOTES ON A CASE OF LEUCOCYTHÆMIA. [MARCH 25, 1882.

throw some light upon both points.

The patient, a well-built man, twenty-nine years of age, came to my friend Mr. Hoare complaining of a large tumour, which extended across his abdomen from the right costal border to the left anterior superior spine of the ilium. This proved upon examination to be an enormously hypertrophied spleen, the hilum being represented by a deep notch a little above the level of the umbilicus. The account of the

the course of a few weeks. On examining the blood under the microscope we found that the leucocytes were enormously increased in number, almost filling up the interspaces of the rouleaux, while the coloured corpuscles were ill-formed, and diminished not only relatively, but also in the aggregate. The proportion of white to red was calculated at one to seven. None of the other blood glands were affected, and

fourteen to eleven stone in a few weeks. Having given both iron and quinine a fair trial, and found them equally ineffectious, we have now had recourse to arsenic in large doses, in combination with the iodide and chlorate of potash. This mode of treatment, combined with a liberal diet, and strict attention to the state of the bowels, has been remarkably efficacious. The tumour has already diminished in size, and some of the more distressing secondary symptoms have been alleviated. The principal interest of the case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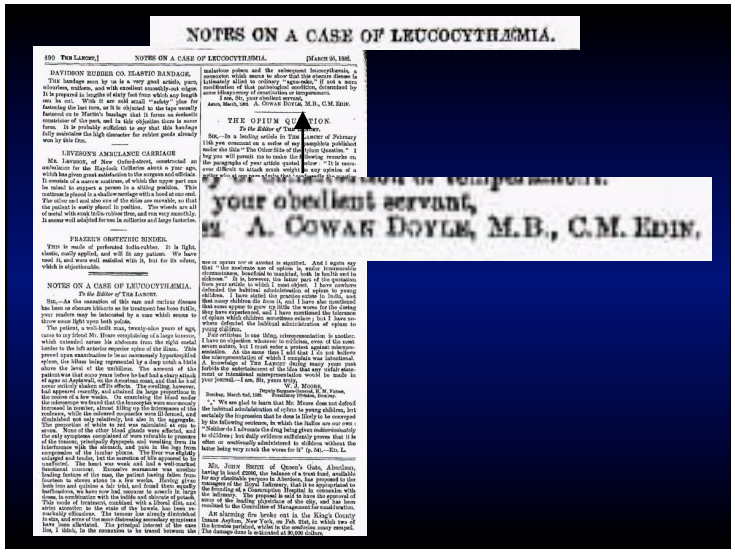
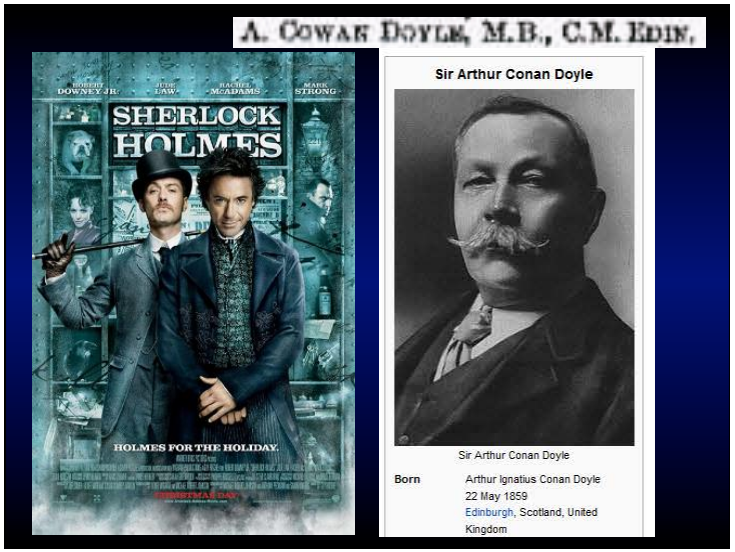

NOTES ON A CASE OF LEUCOCYTHÆMIA.

your obedient servant,

A. COWAN DOYLE, M.B., C.M. EDIN.


A. COWAN DOYLE, M.B., C.M. EDIN.

Sir Arthur Conan Doyle

Sir Arthur Conan Doyle

Born Arthur Ignatius Conan Doyle
22 May 1859
Edinburgh, Scotland, United Kingdom

Arsenicals in the treatment of leukaemia

1878: Boston City Hospital
"leucocythaemia"
1931: Boston City Hospital
chronic myeloid leukaemia
1937: JAMA
chronic myeloid leukaemia

Since then, As_2O_3 was regarded as a standard treatment for leukaemia, there being few effective alternatives

As_2O_3 treatment of leukaemia

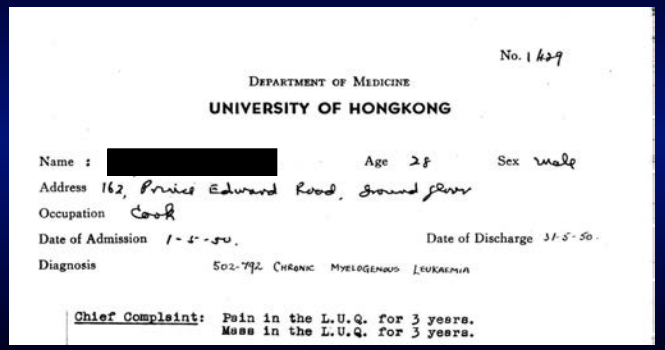
Department of Medicine
University of Hong Kong

In the late forties to early fifties: a standard treatment for leukaemia

Effective in suppressing white cells
Cumulative toxicities included
Skin pigmentation, chronic GI blood loss

Hong Kong Museum of Medical Sciences

Medical records in 1950



No. 1429

DEPARTMENT OF MEDICINE
UNIVERSITY OF HONGKONG

Name : [redacted] Age 28 Sex male
Address 162, Prince Edward Road, Ground floor
Occupation Cook
Date of Admission 1-5-50. Date of Discharge 31-5-50.
Diagnosis 502-792 CHRONIC MYELOGENOUS LEUKAEMIA

Chief Complaint: Pain in the L.U.Q. for 3 years.
Mass in the L.U.Q. for 3 years.

Medical records in 1950

UNIVERSITY OF HONGKONG

Name : [redacted] Age 34 Sex male

Address 142 Prince Edward Road, Second floor

Occupation Cook

Date of Admission 1-2-50. Date of Discharge 14-2-50

Diagnosis Sec. syl. Cutaneo Mucocutaneous Leishmaniasis

Chief Complaint: Pain in the L.U.Q. for 3 years.
Mass in the L.U.Q. for 3 years.

Present Illness:

Patient first noticed pain in the L.U.Q. in 1946. The pain was dull aching in character, having no relation with food, and was not severe at the beginning, but became more marked recently.

At about the same time patient noticed bulging of the left side of the abdomen, and a mass was felt, which increased gradually in size. During this period there was no fever, no jaundice, no bleeding phenomena.

Appetite is not impaired, but patient dared not take too much food, because abdominal discomfort became more marked after a full meal. Micturition no change. No loss of weight noticed.

Past Health: In 1946 patient had attacks of chill and fever intermittently, which responded to quinine. Treatment.
No history of jaundice.
Denied V.D.

Personal History:

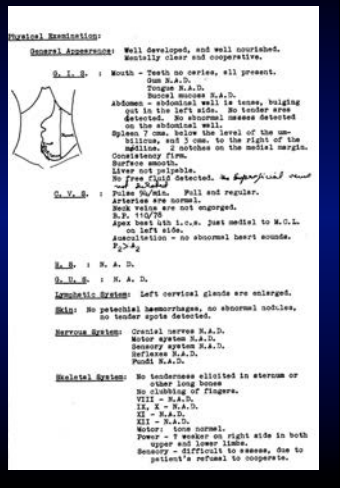
Patient has been a cook in a restaurant for 7 years, before that was an assistant in the kitchen for 3 years.

Patient was born in Hainan, and spent his early days studying in School, never worked in field before. Came to Hong Kong at age of 16 (12 years ago), and was here till 1941, and was in Kweilin, then Loichow, and returned to Hong Kong in 1945.

Family History: Not married.
Father died when he was 3 years old - cause of death he does not know.
Mother still living and well. Now in village.
Brothers.

Social History:

Earning $100.00 per month. Eat and live in the restaurant. Food is very good - fish, meat and vegetables in every meal.



Physical Examination:

General Appearance: Well developed, and well nourished. Mentally clear and cooperative.

E. I. S. : Mouth - Teeth no caries, all present.
Gum N.A.D.
Tongue N.A.D.
Buccal mucosa N.A.D.
Abdomen - abdominal wall is tense, bulging out in the left side. No tender area detected. No abnormal masses detected on the abdominal wall.
Spleen 7 cms. below the level of the umbilicus, and 3 cms. to the right of the midline. 2 notches on the medial margin. Consistency firm.
Surface smooth.
Liver not palpable.
No free fluid detected. No superficial veins dilated.

C. V. S. : Pulse 96/min. Full and regular.
Arteries are normal.
Neck veins are not engorged.
B.P. 110/70
Apex beat 4th I.C.S. just medial to M.C.L. on left side.
Auscultation - no abnormal heart sounds.
$P_2 > A_2$

R. S. : N. A. D.

G. U. S. : N. A. D.

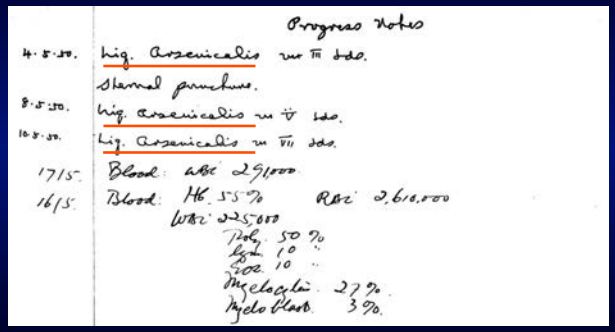
Lymphatic System: Left cervical glands are enlarged.

Skin: No petechial haemorrhages, no abnormal nodules, no tender spots detected.

Nervous System: Cranial nerves N.A.D.
Motor system N.A.D.
Sensory system N.A.D.
Reflexes N.A.D.
Fundi N.A.D.

Skeletal System: No tenderness elicited in sternum or other long bones
No clubbing of fingers.
VIII - N.A.D.
IX, X - N.A.D.
XI - N.A.D.
XII - N.A.D.
Motor: tone normal.
Power - ? weaker on right side in both upper and lower limbs.
Sensory - difficult to assess, due to patient's refusal to cooperate.

Medical records in 1950



Progress Notes

4.5.50. Liq. Arsenicalis m̄ III tds.
Sternal puncture.
8.5.50. Liq. Arsenicalis m̄ V tds.
10.5.50. Liq. Arsenicalis m̄ VII tds.
17/5 Blood: WBC 29,000
16/5 Blood: Hb. 55% RBC 2,610,000
WBC 22,500
Poly. 50 %
Lymph. 10 "
Eos. 10 "
Myelocytes 27 %
Myeloblasts 3 %

Liquor arsenicalis

As_2O_3 treatment of leukaemia

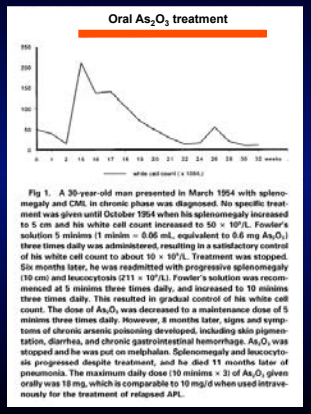


Fig 1. A 30-year-old man presented in March 1954 with splenomegaly and CML in chronic phase was diagnosed. No specific treatment was given until October 1954 when his splenomegaly increased to 5 cm and his white cell count increased to 50 × 10^9/L. Fowler's solution 5 minims (1 minim = 0.06 mL, equivalent to 0.6 mg As_2O_3) three times daily was administered, resulting in a satisfactory control of his white cell count to about 10 × 10^9/L. Treatment was stopped. Six months later, he was readmitted with progressive splenomegaly (10 cm) and leucocytosis (211 × 10^9/L). Fowler's solution was recommenced at 5 minims three times daily, and increased to 10 minims three times daily. This resulted in gradual control of his white cell count. The dose of As_2O_3 was decreased to a maintenance dose of 5 minims three times daily. However, 8 months later, signs and symptoms of chronic arsenic poisoning developed, including skin pigmentation, diarrhea, and chronic gastrointestinal hemorrhage. As_2O_3 was stopped and he was put on melphalan. Splenomegaly and leucocytosis progressed despite treatment, and he died 11 months later of pneumonia. The maximum daily dose (10 minims × 3) of As_2O_3 given orally was 18 mg, which is comparable to 10 mg/d when used intravenously for the treatment of relapsed APL.

As_2O_3 treatment was effective for different types of leukaemia, and may be related to an intrinsic toxicity of As_2O_3 to marrow cells

Resurgence of the use of As_2O_3 in China

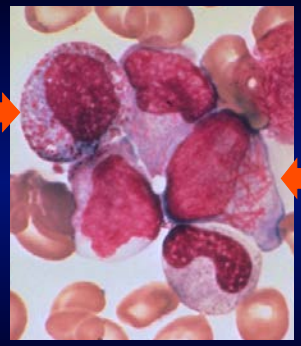
1984 : Zhang TD. Ai Ling No. 1

1988 : Li et al. Treatment of lymphoma

1992 : Sun et al. Ai Lin 1 in acute promyelocytic leukaemia (APL)

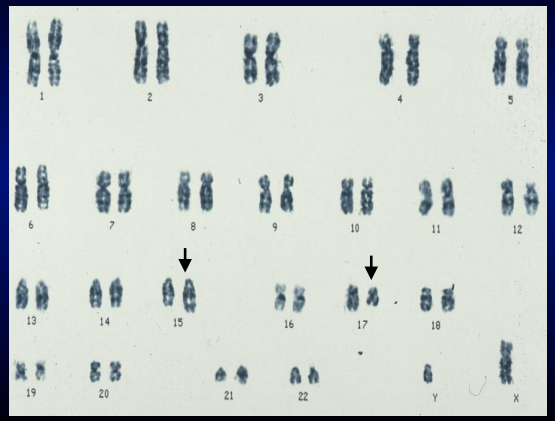
1997 : Chen et al. intravenous As_2O_3 in APL

Acute promyelocytic leukaemia



Faggot: Bundle of sticks or twigs

t(15;17) in acute promyelocytic leukaemia



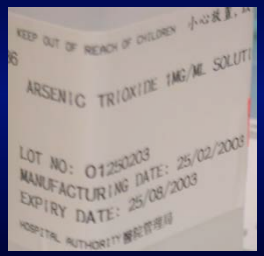
Oral As_2O_3

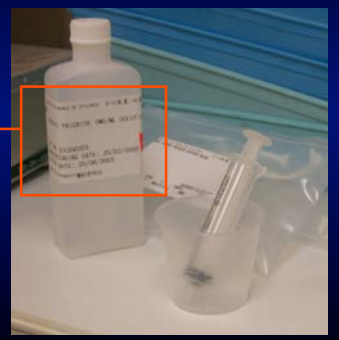
Preparation of an oral formulation

- In collaboration with the Division of Clinical Pharmacology, Department of Medicine, and Pharmacy, Queen Mary Hospital

- Clinical trial started in 2000 for the treatment of relapsed APL

Oral As_2O_3 for treatment of relapsed APL





Oral As_2O_3 therapy in leukaemia

Table 1. Clinicopathologic features and outcome of 12 consecutive patients with relapsed-acute promyelocytic leukemia treated with oral As_2O_3

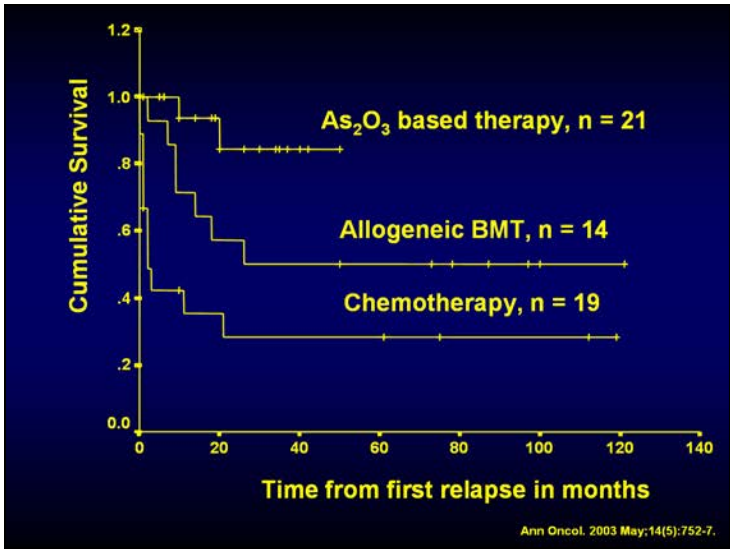
Patient no.	Sex/ age, y	Status	Previous induction treatment	Time from last CR, mo	Relapse Hb, g/L	Relapse WBC, × 10⁹/L	Relapse Plat, × 10⁹/L	Oral As_2O_3 therapy Duration, d	Oral As_2O_3 therapy Additional Rx	Oral As_2O_3 therapy Result	Consolidation	Latest PCR† (mo)	DFS, mo	Remarks
1*	M/23	R1	ATRA + Dauno	11	156	2.1	87	59	Ida	CR	Ida		13	—
		R2	IV As_2O_3 + Ida	10	140	2.5	25	76	ATRA	NR	—	+ (dead)		—
2*	M/33	R2	Dauno/IV As_2O_3 + Ida	25	134	2.1	20	32	ATRA	CR	As_2O_3 + ATRA	− (18)	19+	—
3*	F/13	R2	ATRA + IV As_2O_3	12	86	1.2	15	30	ATRA	CR	As_2O_3 + ATRA	− (18)	19+	—
4	M/54	R1	ATRA + Dauno	100	85	34.9	81	40	Ida	CR	Ida	− (18)	18+	Mother: AML
5*	M/32	R1	ATRA + Dauno + MP	22	145	2.4	177	33	NA	CR	Ida	− (18)	18+	—
6	F/32	R1	ATRA + Dauno	12	122	0.8	84	51	NA	CR	Ida	− (12)	18+	—
7*	F/45	R2	ATRA + Dauno/IV As_2O_3 + Ida	17	112	1.9	50	37	ATRA	CR	As_2O_3 + ATRA	− (14)	17+	—
8	F/65	R1	ATRA	16	72	2.8	141	28	NA	CR	As_2O_3 + ATRA	− (12)	15+	CRF due to DM on CAPD; Ida consolidation omitted due to CRF
9	F/18	R2	ATRA + Dauno/IV As_2O_3 + Ida	12	101	1.9	180	28	ATRA	CR	As_2O_3 + ATRA	− (12)	14+	—
10*	F/18	R1	ATRA + Dauno	12	82	12.6	54	44	Ida	CR	Ida	− (6)	9+	—
11*	M/45	R1	ATRA + Dauno	240	42	0.6	9	22	NA	CR	As_2O_3	− (3)	7+	Ida consolidation omitted due to high cumulative doses of anthracycline
12	F/40	R1	ATRA + Ara-c	23	85	6.5	39	28	Ida	CR	Ida	− (3)	6+	CRHD, double valve rep

DFS indicates disease-free survival; M, male; R1, first relapse; ATRA, all-*trans* retinoic acid; Dauno, daunorubicin; Ida, idarubicin; CR, complete remission; —, none; IV, intravenous; R2, second relapse; NR, nonremission; F, female; AML, acute myeloid leukemia; NA, no additional Rx; CRF, chronic renal failure; DM, diabetes mellitus; CAPD, continuous ambulatory peritoneal dialysis; Ara-c, cytosine arabinoside; CRHD, chronic rheumatic heart disease; and rep, replacement.

*Pharmacokinetic data of oral As_2O_3 have previously been reported.[4]

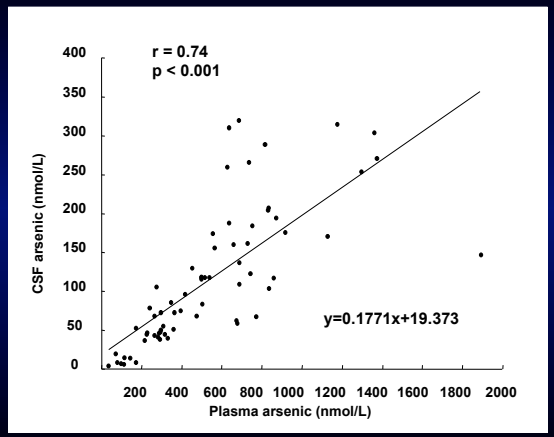
†PCR for *PML/RARA*. + indicates positive; −, negative, (time from initial diagnosis).

Blood. 2003 Jul 1;102(1):407-8.



Ann Oncol. 2003 May;14(5):752-7.

Arsenic penetrates the cerebrospinal fluid



Blood. 2008 Nov 1;112(9):3587-90.

Oral As_2O_3 in pediatric patients

TABLE I. Clinicopathologic Features of Four Children With Relapsed APL

Case	Sex	Age	Hb	WBC	Plat	Induction therapy	Consolidation and Maintenance	Relapse time	First salvage
1	F	3	8.8	20.1	21	ATRA, Dauno, Ara-C	Dauno, Ara-C, amsacrine, VP16 then ATRA, 6-MP, MTX	38 m	Oral-As_2O_3
2	F	10	10.4	101.0	5	ATRA, Dauno, Ara-C	Nil[a]	24 m	Oral-As_2O_3
3	F	13	10.0	1.2	51	ATRA[b]	Nil[b]	12 m	Intravenous-As_2O_3 for 30 days to a cumulative dose of 180 mg, which resulted in CR2 for 14 m before R2
4	F	11	5.6	1.7	14	ATRA, Dauno, Ara-C, VP16	Dauno, Ara-C, VP16[c]	29 m	Intravenous-As_2O_3 for 120 days to a cumulative dose of 755 mg, together with FLAG ×2 courses, which resulted in morphologic CR2 for 8 m with persistent positivity for *PML-RARA*

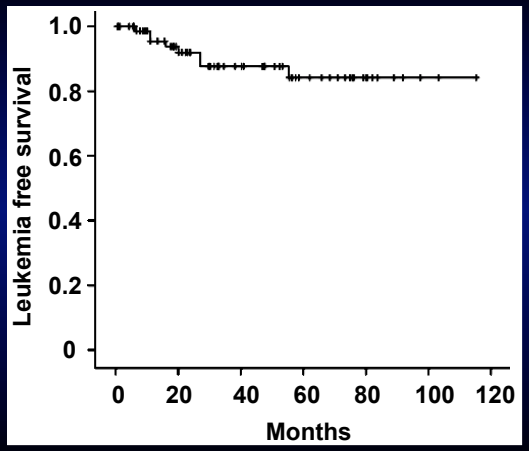
TABLE II. Four Children With Relapsed APL Treated With Oral As_2O_3-Based Regimen

Case	Hb	WBC	Plat	Oral As_2O_3	ATRA	Peak WBC	Side effects	Result	Consolidation	Maintenance	Outcome
1	11.1	2.5	95	3 mg/day × 44	20 mg/day × 14	7.5	Nil	CR2	As_2O_3 + ATRA	As_2O_3 + ATRA × 2 years	MR, 10 m+
2	11.4	4.1	16	5 mg/day × 56	Nil	5.6	Nil	CR2	IDA, IT MTX + Ara-C	Nil	MR, 131 m+
3	11.2	0.8	132	6 mg/day × 42	40 mg/day × 42	2.2	Nil	CR3	As_2O_3 + ATRA	Nil	MR, 132 m+
4	10.1	1.7	44	10 mg/day × 42	60 mg/day	54.0	Nil	CR3	As_2O_3 + ATRA	As_2O_3 + ATRA × 2 years	MR, 114 m+

Hb, hemoglobin (g/dl); WBC, white cell count ($\times 10^9$/L); Plat, platelet count ($\times 10^9$/L); CR, complete remission; MR, molecular remission, m, months.

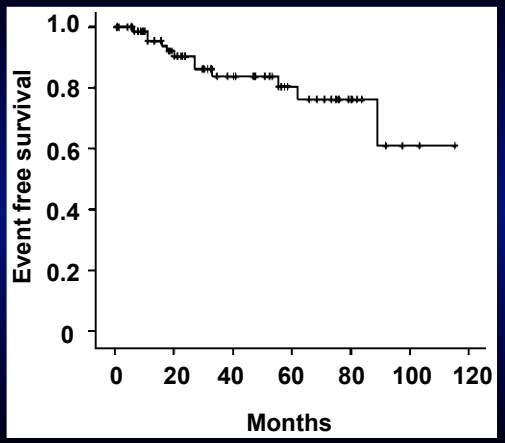
Pediatr Blood Cancer. 2011 Sep 2. [Epub ahead of print]

Oral-As_2O_3 maintenance of 76 APL patients in CR1



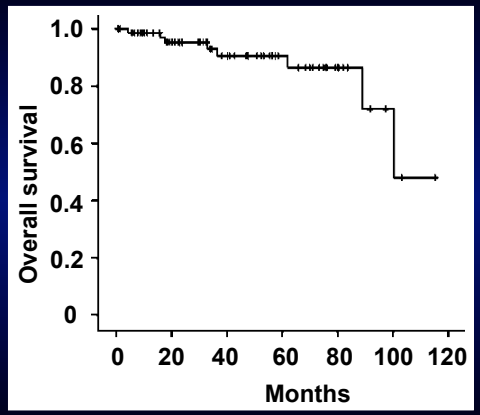
Blood. 2011 Oct 12. [Epub ahead of print]

Oral-As_2O_3 maintenance of 76 APL patients in CR1



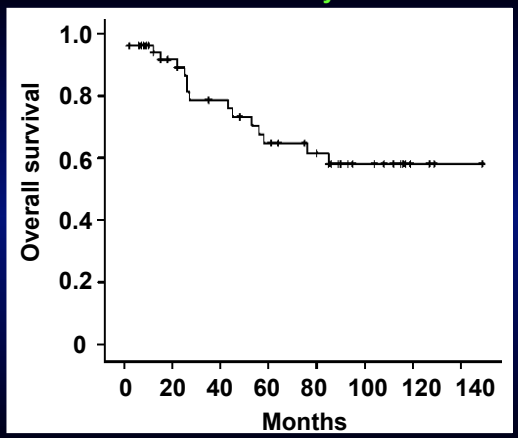
Blood. 2011 Oct 12. [Epub ahead of print]

Oral-As_2O_3 maintenance of 76 APL patients in CR1



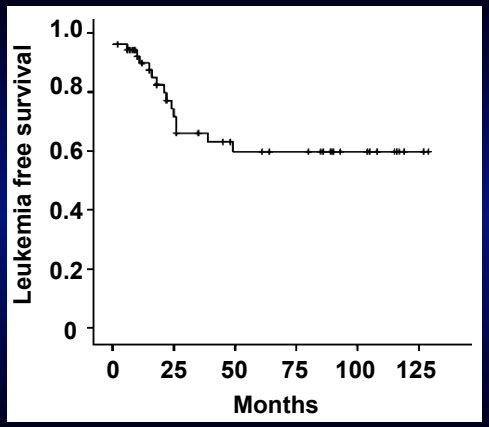
Blood. 2011 Oct 12. [Epub ahead of print]

Oral-As_2O_3 for maintenance of 52 patients with APL in CR2 and beyond



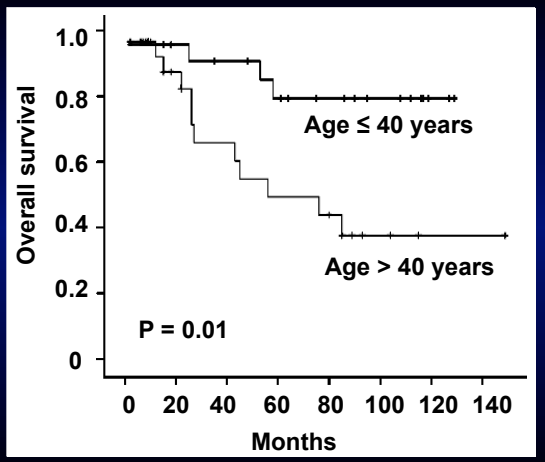
Au et al J-Cin-Oncol 2011 (submitted)

Oral-As_2O_3 for maintenance of APL in CR2 and beyond



Au et al J-Cin-Oncol 2011 (submitted)

Oral-As_2O_3 for maintenance of APL in CR2 and beyond



Au et al J-Cin-Oncol 2011 (submitted)

US007521071B2

(12) **United States Patent**
Kumana et al.

(10) **Patent No.: US 7,521,071 B2**
(45) **Date of Patent: Apr. 21, 2009**

(54) **FORMULATION OF ORAL COMPOSITIONS COMPRISING ARSENIC TRIOXIDE AND METHODS OF USE THEREOF**

(75) Inventors: **Cyrus Rustam Kumana**, Pokfulam (HK); **Yok-Lam Kwong**, Pokfulam (HK)

(73) Assignee: **Versitech Limited** (HK)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 600 days.

(21) Appl. No.: **10/669,869**

(22) Filed: **Sep. 23, 2003**

(65) **Prior Publication Data**

US 2004/0126434 A1 Jul. 1, 2004

Related U.S. Application Data

Kumana, C.R. et al., "Systemic availability of arsenic from oral arsenic-trioxide used to treat patients with hematological malignancies", *Eur J Clin Pharmacol*, 58:521-526 (2002).

Siu, Chung-Wah et al., "Effects of oral arsenic trioxide therapy on QT intervals in patients with acute promyelocytic leukemia: implications on long-term cardiac safety", *Blood*, 0:2006-01-0054 (2006).

Abroun, et al., "Receptor synergy of interleukin-6 (IL-6) and insulin-like growth factor-I in myeloma cells that highly express IL-6 receptor alpha [corrected]", *Blood*, 103(6):2291-8 (2004).

Akay and Gazitt, "Arsenic trioxide selectively induces early and extensive apoptosis via the APO2/caspase-8 pathway engaging the mitochondrial pathway in myeloma cells with mutant p53", *Cell Cycle*, 2(4):358-68 (2003).

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特　許　証
(CERTIFICATE OF PATENT)

特許第４７８６３４１号
(PATENT NUMBER)

発明の名称
(TITLE OF THE INVENTION)
三酸化ヒ素を含む経口組成物の処方およびその使用法

特許権者
(PATENTEE)
香港ボクフラム・ロード、ザ・ユニバーシティ・オブ・ホンコン、ファイナンス・オフィス
国籍　香港
バーシテック・リミテッド

Different generations of As_2O_3

Oral Arsenic trioxide

Arsenic patent (Nature Medicine, October 2007)

Arsenic patent keeps drug for rare cancer out of reach of many

For thousands of years, arsenic has been known to have medicinal properties. It has been used at various times to treat syphilis and sleeping sickness, or occasionally to poison unsuspecting rats and husbands.

In the past few decades, some scientists have discovered arsenic's ability to cure acute promyelocytic leukemia (APL), a rare and fatal cancer that strikes relatively young people.

But despite its abundance and long history, arsenic treatment is inaccessible to all but the richest of people—because an American company holds the patent on a drug called Trisenox, a soluble form of arsenic trioxide.

Pharmaceutical companies point to the high cost of research and development as the reason for exorbitant drug prices. But in this case, critics charge, little research was necessary, and the patent that keeps the price high should never have been granted.

"When you have a miracle drug and it's not used, it's unacceptable," says Hugues de Thé, professor of molecular biology at the University of Paris, who has worked on arsenic therapy for more than 15 years. "I would never have even they did not describe the recipe in the literature, Warrell says, they left the door open for someone else to make a patentable formula.

It took no more than a couple of months for Warrell's group to make its own soluble arsenic trioxide. The results matched the success reported in China. In 1998, Warrell and his colleagues filed a patent for their formulation and launched a company dubbed PolaRx (*N. Engl. J. Med.* 339, 1341–1348; 1998).

Because arsenic is toxic to animals, the researchers had trouble finding companies to develop the drug, but based partly on the Chinese results, they convinced the US Food and Drug Administration to allow a small clinical trial. "We agreed to give day-to-day feedback," Warrell says.

In 2000, Seattle-based Cell Therapeutics acquired PolaRx, including its arsenic trioxide patents, for $15 million in stock. "It was practically nothing—an embarrassing amount," says Warrell, who says he receives "a small amount" in royalties. In June 2005, Cell Therapeutics sold the drug to Pennsylvania-based Cephalon for $70 million.

to buy the drug, according to Ali Bazarbachi, a medical professor at the American University of Beirut. The drug is also awaiting approval in Brazil, where its high price is likely to make it a last resort for those who fail treatment with other alternatives.

"Many hematologists around the world, including in Europe, think that both the patent and the price of arsenic are outrageous," says Bazarbachi.

Desperate for the drug, some countries are looking to scientists in Iran, where the patent is not valid, to produce the drug cheaply. Cephalon is also working with various countries to set up compassionate use programs. "It is not Cephalon's intent or practice to keep products away from patients in need," says Candace Steele, a spokeswoman for the company.

Because APL affects only two people in a million on average, and because there are other alternatives, such as retinoic acid, available—albeit with more side effects—arsenic is unlikely to become the focus of a large lobby group in any country.

In the meantime, arsenic is finding wider

Arsenic patent (Nature Medicine, October 2007)

thought about patenting a drug that is 3,000 years old," de Thé says. "The idea that this drug is not used drives me crazy."

Arsenic's use to treat APL began in the 1970s, when researchers at Harbin Medical University in northeast China used a crude mix of arsenic trioxide and mercury to treat various cancers. But the work did not attract broader attention until the early 1990s, when it was published in a Chinese journal (*Chin. J. Intergr. Med.* 12, 170–171; 1992). In their study, the researchers found that arsenic trioxide brought on complete remission for about two-thirds of those with APL.

In 1996, the researchers collaborated with another team at the Shanghai Second Medical University, led by the current Chinese Health Minister Zhu Chen, and presented the results to an international audience (*Blood* 89, 3345–3353; 1997).

Raymond Warrell, chairman of the New Jersey–based company Genta Incorporated, recalls that when he reviewed the *Blood* article for publication, he recommended that it should be accepted "with extremely high priority."

But the Chinese group did not, as the reviewers had requested, describe how they had produced the arsenic they used, says Warrell, who was then a researcher at the Memorial Sloan-Kettering Cancer Center in New York.

The Chinese researchers had learned how to produce an inorganic, stable, soluble form of arsenic, which is generally insoluble. But because

Still, at up to $50,000 for a full course, Trisenox is out of reach for most people in developing countries.

"Without the patent, it would have remained a curious Chinese drug, not available to anyone else," he says. "Most of the patients are young, and it gives them another 60 years of life. Relative to the benefit, it's cheap."

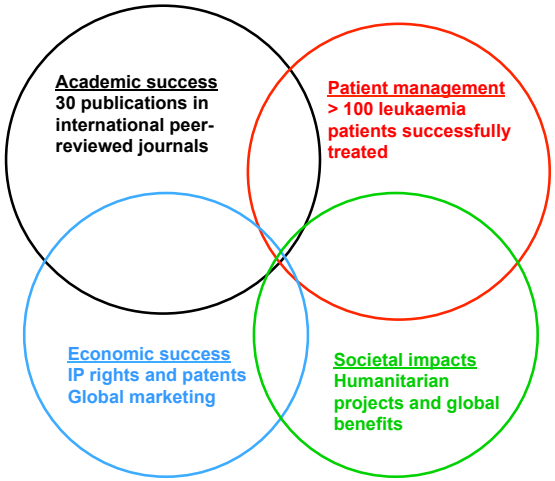
Still, at up to $50,000 for a full course, Trisenox is out of reach for most people in developing countries.

In Lebanon, for example, where the average income is $5,000 per year, it has been prescribed to just five people over the past two years. Four of them recovered from the cancer. The fifth died because his illness had progressed too far while he tried to raise money

Sweet poison: The high price of an arsenic-based cancer drug is "outrageous", says Lebanese scientist Ali Bazarbachi.

2010 International Arsenic Union

A success paradigm of medical research



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