HKU Successfully Developed Oral Arsenic Trioxide as The First Ever Patented Prescription Drug in Hong Kong
A success Story of Hong Kong Innovation

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Section 1
By Professor CR Kumana & Professor YL Kwong

1. Introduction
2. Development of Oral Arsenic Trioxide

Arsenic

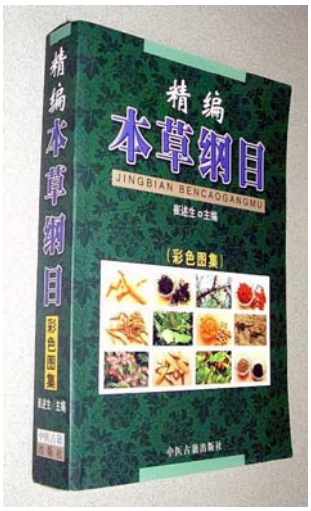
Medicinal use of arsenic has been known for centuries in China and medieval Europe

Arsenic in Chinese Medicine

The use of arsenic compounds has been described for over 2,000 years

神農本草經卷二中經玉石中品
李時珍本草綱目

Materia Medica (Li ShiZhen) Ming Dynasty, 1577



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"。

Description of Arsenic sulphide in Shen Nong's Herbal Classic and Compendium of Materia Medica

雄黃：神農本草經卷二中經玉石中品早列雄黃為藥物，主治"寒熱，鼠瘘惡瘡，疽痔死肌，殺精物惡鬼邪氣百蟲毒"。明李時珍本草綱目指雄黃能"治緩疽惡瘡，蝕惡肉"，為"治瘡殺毒要藥也"，而"肝風肝氣，驚癇痰涎，頭痛眩運，暑泄痢，積聚諸病，用之有殊功"。

Description of Diarsenic trisulphide in Shen Nong's Herbal Classic and Compendium of Materia Medica

雌黃：神農本草經卷中經玉石中品早列雌黃為藥物，主治"惡瘡頭禿痂疥"、"殺毒蟲虱"，亦能治"身癢，邪氣，諸毒"。明李時珍本草綱目指雌黃能"治冷痰勞嗽，血氣蟲積，心腹痛，癲癇"

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

Arsenic trioxide

1. **Interests waned after the second world war**
2. **The development of newer anti-cancer agents made arsenic trioxide out of fashion**
3. **No longer described in standard haematology textbooks after 1950**

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. 1 429

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

No. 1 429

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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.

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 1944 patient had attacks of chill and fever intermittently, which responded to Quinine. [illegible]
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 Heinan, and spent his early days studying in Heinan, 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 Luichow, 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 [illegible].

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.

G. 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. The superficial veins not dilated

C. V. S. : Pulse 94/min. Full and regular.
Arteries are normal.
Neck veins are not engorged.
B.P. 110/78
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.

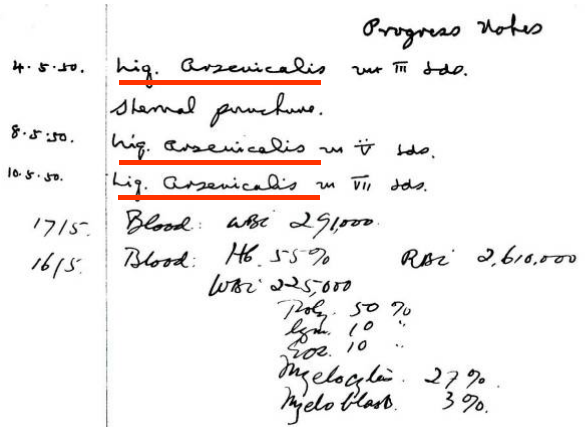
Lymphatic System: Left cervical glands are enlarged.

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 m iii tds.

Sternal puncture.

8.5.50. liq. Arsenicalis m v tds.

10.5.50. liq. Arsenicalis m vii tds.

17/5 Blood: WBC 29,000.

16/5 Blood: Hb. 55% RBC 2,610,000

WBC 225,000

Poly. 50 %

Lym. 10 "

Mon. 10 "

Myelocytes 27 %

Myeloblasts 3 %.

Liquor arsenicalis

As_2O_3 treatment of leukaemia

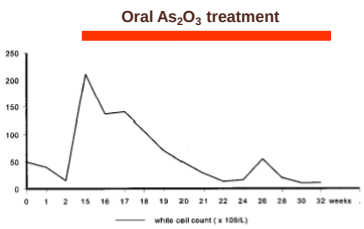


Fig 1. A 30-year-old man presented in March 1954 with splenomegaly and CML in chronic phase was diagnosed. No specific treatment was given until October 1954 when his splenomegaly increased to 5 cm and his white cell count increased to 50 × 10^9/L. Fowler's solution 5 minims (1 minim = 0.06 mL, equivalent 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

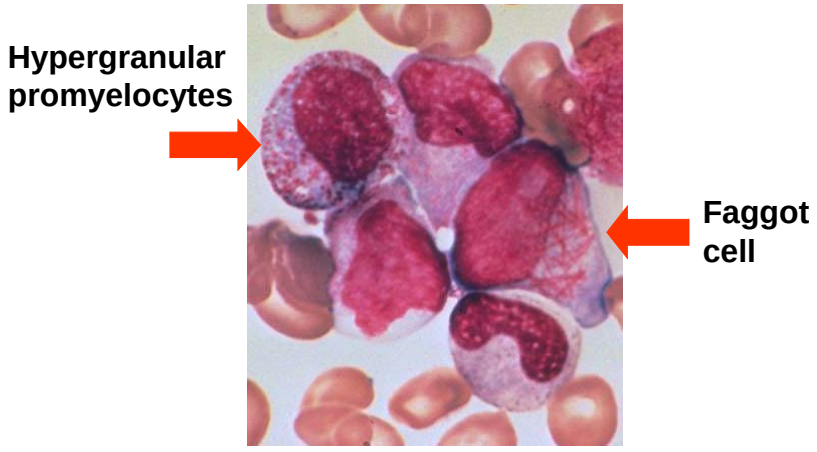
1984 : Zhang TD. Ai Ling No. 1

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

Experience of the use of As_2O_3 at Queen Mary Hospital, Hong Kong

First used in 1996 in relapsed APL (ATRA in 1993 in newly diagnosed APL)

As_2O_3 was originally imported from Shanghai

Very encouraging initial results in relapsed APL

Development of oral As_2O_3 for the treatment of leukaemia

1. As_2O_3 used to be given orally, so an oral solution should be effective
2. Potential concerns of an oral formulation of As_2O_3
- **A. Bioavailability**
- **B. Toxicity (first pass effect) on the liver**

Oral As_2O_3

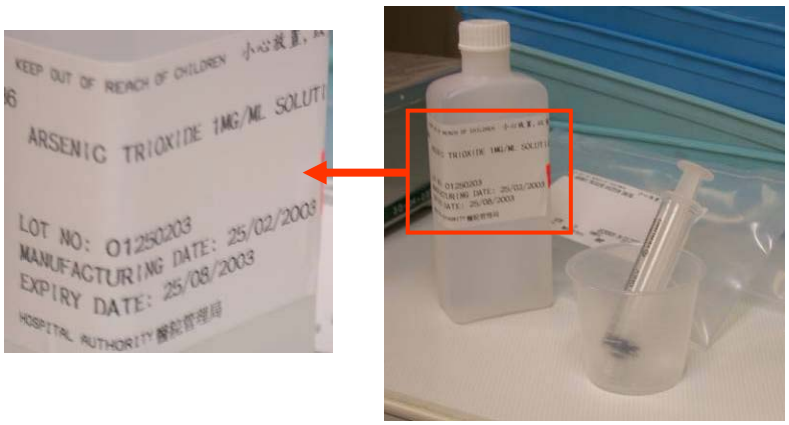
Preparation of an oral formulation

- 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

- Pharmacokinetic studies

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, $\times 10^9$/L	Relapse: Plat, $\times 10^9$/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	34.8	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

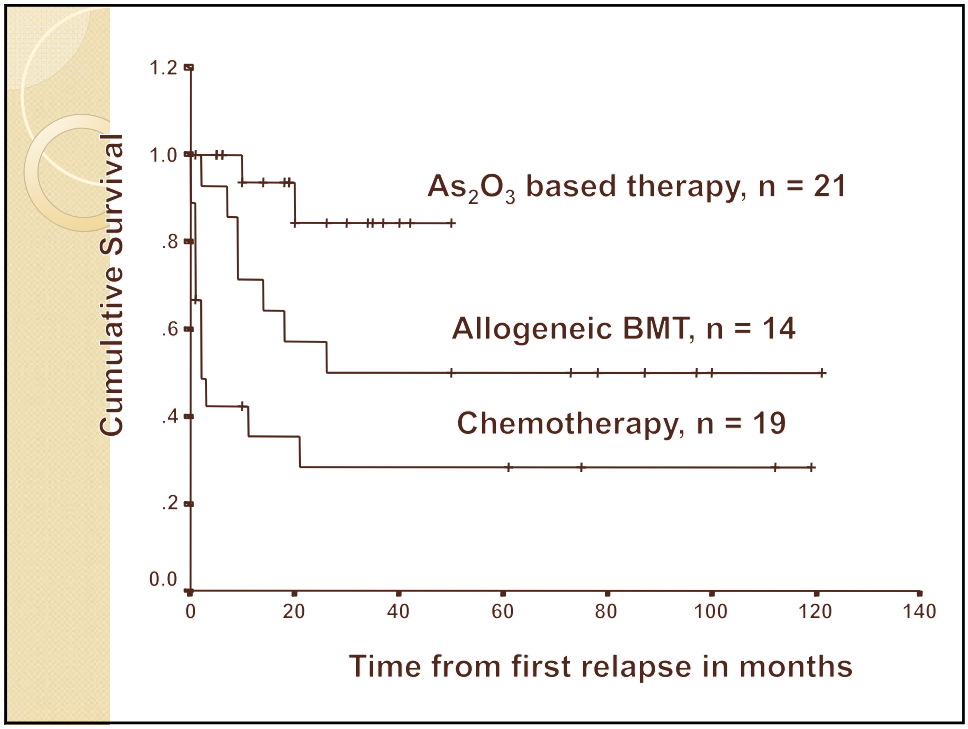
DFS indicates disease-free survival; M, male; R1, first relapse; ATRA, all-*trans* retinoic acid; Dauno, daunorubicin; Ida, idarubicin; CR, complete remission; —, none; IV, intravenous; R2, second relapse; NR, nonremission; F, female; AML; acute myeloid leukemia; NA, no additional Rx; CRF, chronic renal 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]

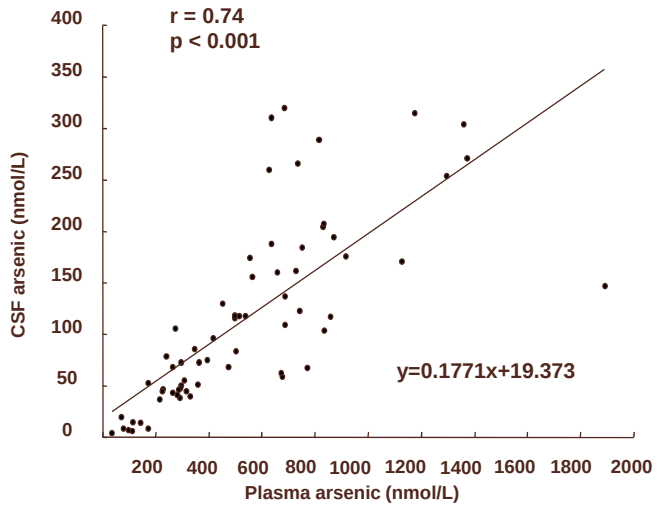
†PCR for *PML/RARA*. + indicates positive; –, negative, (time from initial diagnosis).

As_2O_3 in relapsed APL

1. **High efficacy, almost 100% CR rate**
2. **With maintenance treatment, many patients in fact never relapse**
3. **How does As_2O_3 treatment compare with chemotherapy?**
4. **How does As_2O_3 treatment compare with bone marrow transplantation?**



Arsenic penetrates the cerebrospinal fluid



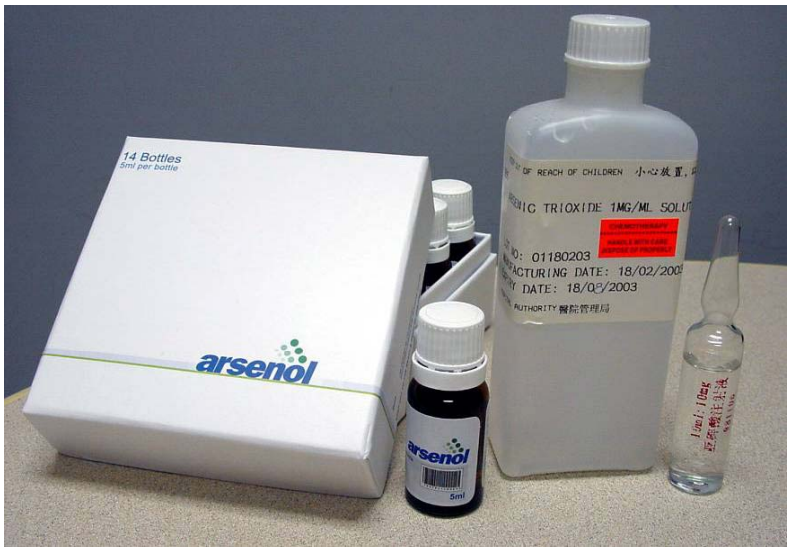
Current status of As_2O_3 in treating cancers at Queen Mary Hospital, Hong Kong

1. APL
   - Maintenance of CR1
   - Treatment of R1 and beyond
2. Multiple myeloma
   - Arsenic as maintenance after mini-allografting
3. Mantle cell lymphoma
   - Salvage treatment
4. Refractory leukaemia and MDS
   - Phase I/II trial

Timeline of the development of oral arsenic trioxide

1998: retrieval of old records, oral formulation worked on
2000: first oral formulation tested in patients
2001: replacement of i.v. As_2O_3 by oral As_2O_3
2002: filing of patent with Versitech, a University of Hong Kong company dealing with technology transfer
2006: Verification of cardiac safety of oral As_2O_3
2007: Production of oral As_2O_3 to GMP standards
2009: US Patent
2010: First international conference of oral arsenic trioxide in Hong Kong

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 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 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.

Under international patent law, according to a Cephalon representative, the basis for the patent is the clinical use of arsenic trioxide and not the chemical itself. But de Thé notes that the clinical efficacy had already been shown by the Chinese. "The patent was taken after all the work was done," de Thé says, adding that making arsenic trioxide soluble "basically means they boiled it."

But Warrell defends the patent, saying that it at least helped generate companies' interest in bringing the drug to market. "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 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 acceptance. At the annual meeting of the American Society of Clinical Oncology in June, Irani researchers presented data from the largest trial to date on arsenic trioxide alone, showing that of 141 individuals with APL treated with the compound, 85% had healed completely.

David Cyranoski, Tokyo

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

Arsenic patent (Nature Medicine, October 2007)

(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**

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Related U.S. Application Data

(60) Provisional application No. 60/417,200, filed on Oct. 9, 2002, provisional application No. 60/483,014, filed on Jun. 25, 2003.

(51) **Int. Cl.**
A61K 33/36 (2006.01)
A61P 7/00 (2006.01)
A61P 35/02 (2006.01)

(52) **U.S. Cl.** **424/623**

(58) **Field of Classification Search** 424/623
See application file for complete search history.

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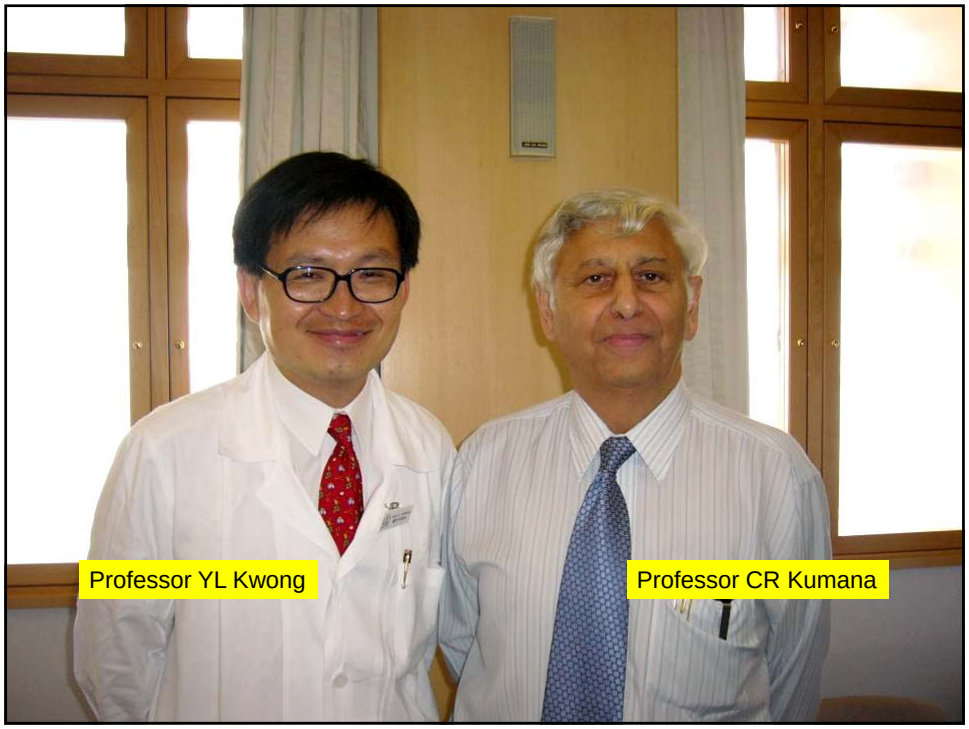

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Section 2
By Dr Au Wing Yan

1. Oral arsenic rescue of APL relapses
2. Oral arsenic prevention of APL relapses
3. Oral arsenic treatment of lymphoma

1. Superiority of oral arsenic trioxide to iv arsenic

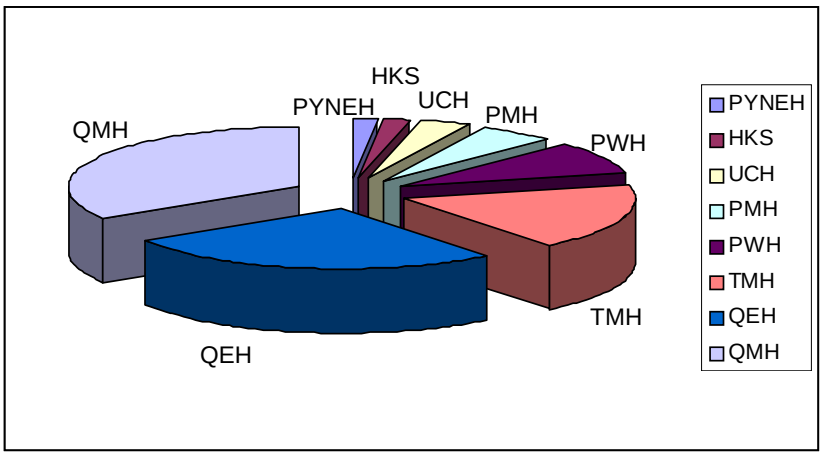
- Arsenic (iv) is universally used for APL relapse
- EXCEPT in Hong Kong, because we have something BETTER, since Oral arsenic means:

1. Out-patient treatment
2. Easy dose titration
3. Negligible cardiac toxicity
4. Long term maintenance possible
5. Massive cost savings

Treatment of APL relapses

- 56 consecutive patients
- 30 men 26 women, average age 39 (range 12 to 72)
- Time from previous remission 19 months (range 6-243)
- Referral from all over Hong Kong
- 53 Chinese, 1 Nepalese, 2 Indonesian

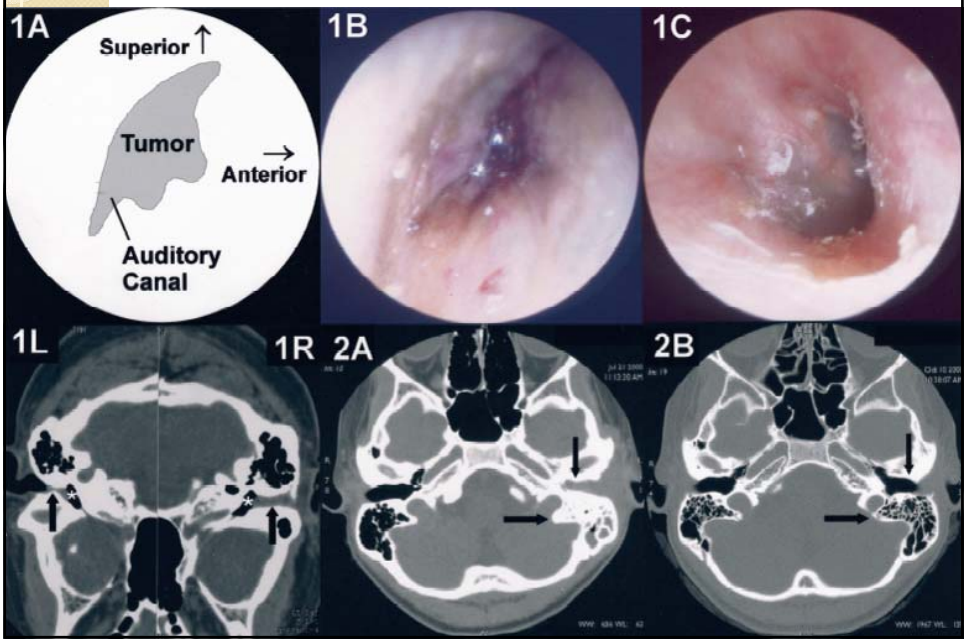
Referrals: APL relapses



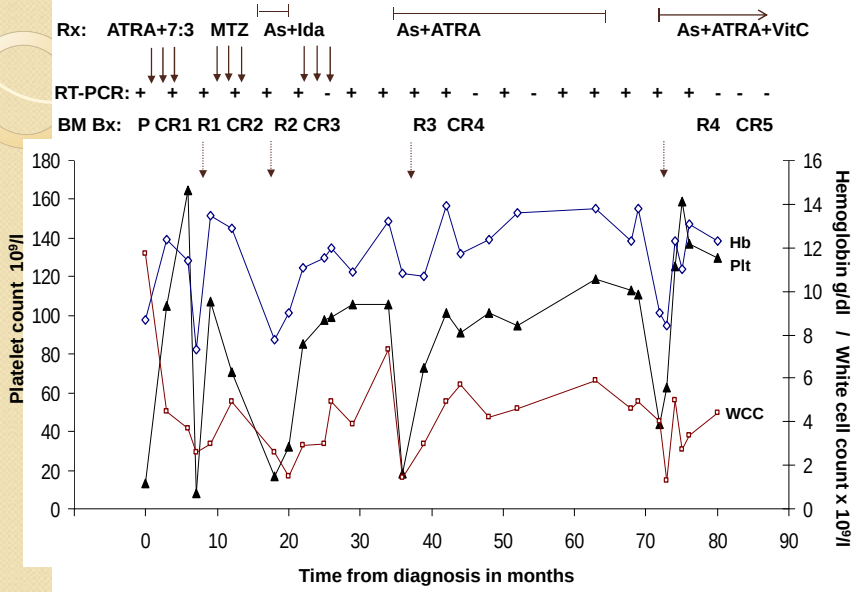
Spectacular results

- Remission again in 55/56 cases (98.2%)
- 6 seniors (age > 60), 3 minors (age 12, 13 and 16)
- 1 Jehovah witness, 1 peritoneal dialysis, 1 tetraplegic, 2 ear relapse,
- With prolonged treatment 5-year survival is 70%
- Cases relapsing after REPEATED chemotherapy may still be CURED with arsenic
- Better than BMT: withhold until further relapses, avoided for most patients
- In other countries, arsenic followed by BMT or antibody treatment or more iv arsenic

Response of ear leukemia to As_2O_3



Chemo-resistant leukemia cured by As_2O_3



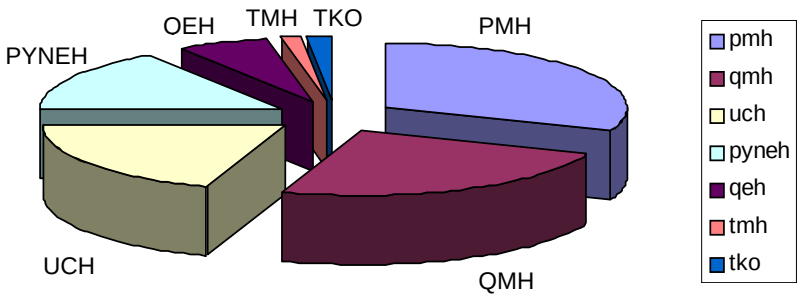
2 .Rationale of arsenic prevention

- **Since arsenic is safe, inexpensive, and convenient, and is synergistic with oral ATRA and Vitamin C (Ascorbic acid, AAA combination)…..**
- **And can cure patient relapsing AFTER intravenous and oral chemotherapy**
- **Why not use it early to prevent relapse?**
- **All countries from USA to China now use iv arsenic to prevent relapse**

Hong Kong arsenic prevention

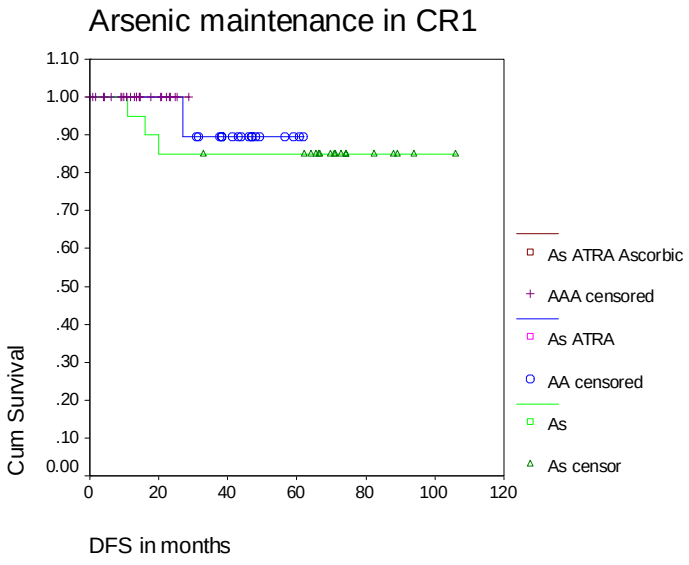
- 65 patients from 2001
- 29 men and 36 women
- Average age 44 (range 16 to 82)
- 12 patients age >60, No chemotherapy AT ALL in 8 of them!
- “Outpatient drink” to treat leukemia at home in elderly, NO nausea, cytopenia, infection, aloplecia, pain, ulcer……

Referrals: Relapse prevention



Outstanding results

- **Median FU 36 months (max 100 months)**
- **Only 5 relapses at 11-27 months (7%).**
- **Three of the 5 relapses respond to arsenic again and are now in remission.**
- **No relapses so far with AAA combination**
- **Future challenge, cerebral disease in patients with high white cell counts.**



No more chemo for APL in elderly!

3. Arsenic for lymphoma

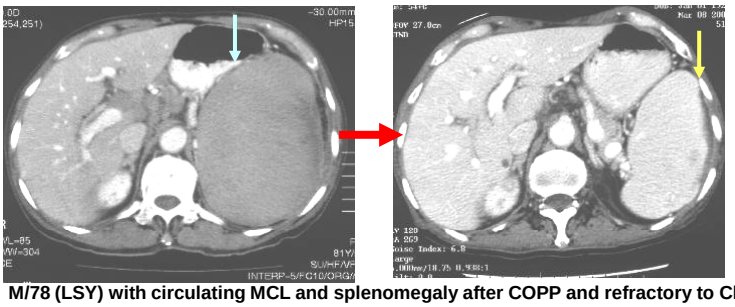
- **Lots of in vitro experiments showing arsenic work for lymphoma cell lines.**
- **In 2 patients with APL and indolent lymphoma, the use of oral arsenic successfully controlled both diseases and prevented follicular and mantle cell lymphoma relapse!**

Mantle cell lymphoma

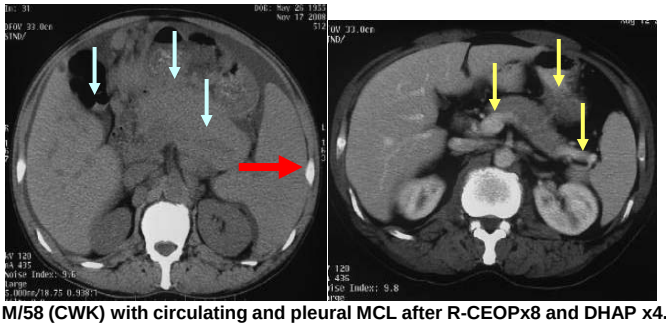
- Refractory lymphoma with median survival of 3-5 yr.
- No cure without allo-BMT
- Chemo-refractory when late
- New agents against MCL may be useful for short time (~6 months) and are very expensive

Arsenic treatment of MCL

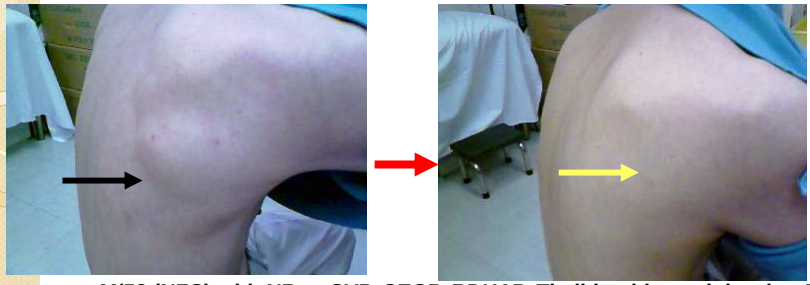
- There were 20 men and 5 women (median age 65 range 43-90). Time from diagnosis was 33 (6 - 131) months, had 2 (1 to 6) treatments before.
- A total of 16 patients (61%) responded (8 CR / CRu, 8 PR) lasting median 23 (6 to 76+) mo. before progression.
- 12 patients still in disease control, longest remission 76 months.
- Synergism with oral alkylator pills, takes time to respond, make disease static, can retreat at relapse



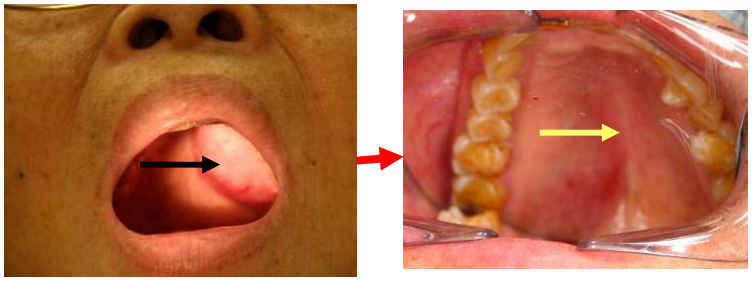
M/78 (LSY) with circulating MCL and splenomegaly after COPP and refractory to Clb, treated with Vit C and Clb, with arsenic at 6 months, respond x 14 months.



M/58 (CWK) with circulating and pleural MCL after R-CEOPx8 and DHAP x4. Regression of LN, ascites, hepatosplenomegaly and normal CBP at 6 months of arsenic and Clb and stable at 14mo on arsenic only.

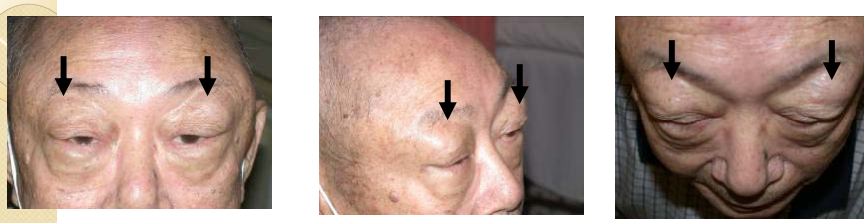


M/53 (NZC) with NR to CVP, CEOP, RDHAP, Thalidomide, and develop RT related sarcoma as well. Regression of back mass after 3 mo. arsenic, Vit C and Clb. Die leukemic relapse at 8 mo.

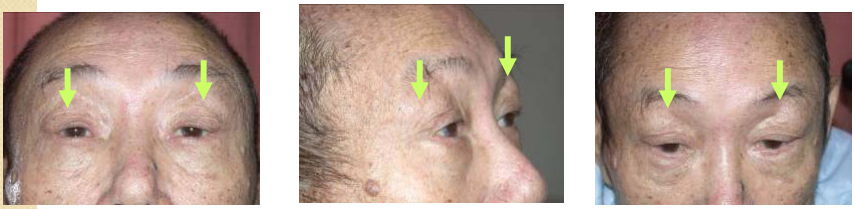


F/65 (TCK) relapse with RT, COPP, CHOP, DHAP. Regression of palate mass at 6 months with oral arsenic, Vit C and Clb, maintained on oral arsenic x 2 years.

Regression of orbital infiltrate



After 4 months of treatment



M/76 (WCF) bilateral orbital MCL relapse after CEOPx7, IMVPx3. Regress after oral arsenic, Vit C and Clb, maintained on oral arsenic x 2 years. Relapse 3.5 years later, retreated and re-responded

Recap

1. Oral arsenic should replace iv arsenic for rescue of APL relapses
2. Oral arsenic can be used BEFORE relapse or even with no chemotherapy for prevention of APL relapses
3. Oral arsenic treatment has powerful utility for treatment of lymphoma, especially mantle cell lymphoma

We are on a mission to change world therapeutic practices

2010 International Oral Arsenic Union
38th Annual Scientific Meeting of HK Society of Hematology

Hong Kong SAR China
Deadline for submission of abstracts
撮要投稿截止日期 31 December 2009
Deadline for corporate registration
團體註冊截止日期 15 January 2010
Deadline for individual registration
個人註冊截止日期 31 December 2009
Date of Congress 會議日期
26 - 27 March 2010
Post Congress symposium Macau
28 - 29 March 2010
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Section 3

By Professor Y.L. Kwong

Overall Conclusion

Oral arsenic trioxide : prescription drug

1. International collaborative trials to define its role in blood cancers, including leukaemias, myelodysplastic syndrome, multiple myeloma and malignant lymphomas
2. Global marketing strategies: Versitech
3. Humanitarian projects of making oral arsenic trioxide available to developing countries

Arsenic trioxide: scientific development

1. Three other patents have been applied for the use of arsenic trioxide in
   A. Solid tumors
   B. Other blood cancers
   C. Non malignant diseases

Achievements of oral arsenic trioxide

1. First prescription drug to be developed entirely in Hong Kong
2. First Hong Kong prescription drug to secure a US patent
3. Puts the Hong Kong team as one of the best in the world in this area of research
4. Humanitarian aid to developing countries to save lives of leukaemia patients
5. Very significant potential financial implications for Hong Kong
6. Paradigm of Hong Kong innovation

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Q&A session