

## 【Management of Arsenicosis】

**S**till now there is no effective treatment of arsenicosis. Even then, scientists and physicians are trying to relieve the symptoms of arsenicosis by reducing body arsenic load as well as complications. Body arsenic load can be reduced by a) stoppage of drinking arsenic contaminated water; b) intake of low arsenic contaminated food; c) avoid inhalation of arsenic contaminated air; and d) take drug that enhances biotransformation and excretion of arsenic. It is always advisable to start the treatment as soon as possible.

Animal model is important to findout an effective drug. However, it is a difficult task to make an animal model of skin manifestations of arsenicosis. Most of the animal studies show the effect of drug in reducing the body arsenic load as well as the evidence of oxidative stress. It has been tried to have animal

model of arsenic-induced cancer.

Only a limited number of studies conducted on human. Some studies are well designed whereas others are not. Based on these limitations, some of the antioxidant vitamins and minerals are suggested to be effective in the treatment of arsenicosis. The use of antioxidant is due to the development of arsenic-induced oxidative stress.

The administration of 1 g of sodium thiosulfate orally or intravenously causes a rapid and pronounced increase in the excretion of arsenic. Its use was first introduced by Paul Who is the Reader?

Doctor working in the arsenic endemic area will be the reader of this book.

(Ravaut, 1920). The oral administration of sodium thiosulfate (20 and 40 g) significantly decreased the arsenic load in milk, urine, and hair of cattle in arsenic endemic area after 1 month of treatment (Ghosh et al., 2011). It can also be administered intravenously and has adverse effects like nausea, joint pain, muscle cramp, blurred vision, agitation, and hallucinations.

The use of chelating agents like dimercaptosuccinic acid (DMSA), 2, 3-dimercapto-1-propanesulfonate (DMPS), dimercaprol (British anti-Lewisite; BAL) and d-penicillamine is effective in acute arsenic poisoning. However, their role in the treatment of arsenicosis remains inconclusive due to inadequate studies on patient. Major drawbacks of dimercaprol include (a) its low therapeutic index, (b) its tendency to redistribute arsenic to brain and testes, for example, (c) the need for intramuscular injection which is painful and (d) its unpleasant odor. When compared to dimercaprol, DMSA, DMPS were of significant lower toxicity and could be administered orally or intravenously (Aaseth, 1983). A well-designed study using DMSA shows its ineffectiveness in the treatment of arsenicosis (Guha Mazumder et al., 1998). The same

research group conducted another study which shows significant improvement in the clinical score of patients suffering from arsenicosis by administering DMPS (Guha Mazumder et al., 2001). This effect may be due to increased urinary excretion of arsenic during the period of therapy.

## 10.1 Non-malignant Skin Manifestations

*Treatment of melanosis:* Stoppage of drinking arsenic contaminated water is effective in the treatment of melanosis. However, it recurs when a patient starts to drink arsenic contaminated water again. In some of the arsenic endemic areas, almost all the hand pump tube wells are contaminated with high concentration of arsenic. In that situation, it is difficult to provide arsenic safe drinking water. In addition, the emphasis should be given on the provision of a diet rich in protein and vitamins. Intake of plenty of green leafy vegetable is advised.

*Chronic Arsenicosis of Cattle in West Bengal and It's Possible Mitigation by Sodium Thiosulfate.*

*Treatment of keratosis:* Stoppage of drinking arsenic contaminated water or shifting of highly arsenic contaminated hand pump tube well to low arsenic contaminated hand pumped tube well is necessary. Keratosis present in the palm and sole can be treated by topical application of salicylic acid with or without urea, propylene glycol, and neem. Orally administered compounds are beta-carotene, retinoid, ascorbic acid, alpha-tocopherol, zinc, selenium, spirulina, alpha-lipoic acid, and folic acid. These are not specific and require longer time to relieve (3-14 months). Among the vegetables, cereals and spices that can be used include: spinach, corn, amaranth leaf, garlic, curcumin and kala jeera oil. Root of water hyacinth is also found to reduce the arsenic load in rat. The use of probiotics is also tried to find out its effectiveness in keratosis.

*Salicylic acid:* Salicylic acid is a keratolytic (peeling agent). It causes shedding of the outer layer of skin. The topical use of 10% boric acid ointment containing 6% salicylic acid in arsenical keratosis for treatment purpose has a long history (Hall, 1946). There was confusion about the percentage of salicylic acid that can be used in arsenical keratosis. Therefore, a randomized control trial on 150 cases with severity of disease (mild, moderate and severe), concentration of salicylate (5, 10, 20 and 30%), and duration of treatment (1, 3 and 6 months) was conducted (Islam et al., 2007). Almost all cases of mild and moderate forms of keratosis were found to be improved (97.6 and 95.0% respectively) whereas severe cases showed comparatively less improvement (67.5%). About 90% improvement was observed using 20 or 30% concentration in mild keratosis within 1 month and 100% improvement with 10, 20 or 30% concentrations within 3 months of treatment. In the case of moderate keratosis, more than 90% improvement was found using 5% concentration or more after 6 months of treatment. More than 90% improvement was noted in the severe form of keratosis only by using 30% concentration salicylic acid for 6 months. For simplicity, it is recommended to use 20% salicylic acid for keratosis.

*Urea:* The urea is an emollient (that is, skin softening agent). It helps to moisturize the skin. The use of urea with salicylic acid is suggested to treat arsenical keratosis. However, salicylic acid should not be used with urea (10-50%). The urea enhances the penetration of salicylic acid and produces the systemic adverse effects of salicylate.

*Propylene glycol:* Propylene glycol is usually used as a dissolving media for paracetamol. A randomized study was conducted on 60 patients of arsenical palmer keratosis treated topically with three different concentrations (15, 30 and 45%) of propylene glycol once daily at both palms at bedtime for eight weeks (Dina & Misbahuddin, 2010). Thirty percent or more concentration of

propylene glycol was effective for mild to moderate form of keratosis. Propylene glycol was well tolerable. Both roughness and thickness of arsenical palmer keratosis can be reduced using propylene glycol and as the concentration of the drug increases, its effectiveness is increased without any significant adverse effect. Therefore, 45% propylene glycol is recommended for topical use in the treatment of arsenical keratosis.

*Neem:* Neem is a plant which is extensively used in different diseases. Topical application of dichloromethane extract of neem (*Azadirachta indica*) once daily (overnight) for 12 weeks showed significant improvement in palmar arsenical keratosis (Ferdous and Misbahuddin, 2014). So, topical application of neem extract may be recommended for the treatment of arsenical keartosis.

*Vitamin A:* The serum concentration of retinol in patients with non-malignant skin lesions is not significantly changed from the control (Chung et al., 2006). However, oral administration of vitamin A (150,000 units) daily for three months was effective in arsenical keratosis following medicinal use of arsenic (Hall, 1946). Open clinical trial on arsenicosis shows its effectiveness when combination of vitamin A, C and E were used.

The main disadvantage of using vitamin A is the longer duration of treatment. The effectiveness of vitamin A does not mean that the patient of arsenical keratosis has avitaminosis, hypovitaminosis or dysvitamino-sis.

*Acitretin:* Acitretin is a second generation retinoid. Combination of low dose acitretin and salicylic acid (16.7%) was also found to be effective (Son et al., 2008).

*Beta-carotene:* beta-Carotene is the precursor of vitamin A. The serum concentration of beta-carotene in patients with non-malignant skin lesions in West Bengal (India) is not significantly changed from the control (Chung et al.,

2006). However, patients of arsenic-induced skin cancer in Taiwan have low level of beta-carotene in blood (Hsueh et al., 1997). beta-Carotene was used with vitamin A, C and E for the treatment of non-malignant skin lesion. However, prolonged use of beta-carotene was found to develop lung cancer. A total of 29,133 male smokers 50 to 69 years of age from southwestern Finland were randomly assigned to one of four regimens: alpha-tocopherol (50 mg per day) alone, beta carotene (20 mg per day) alone, both alpha-tocopherol and beta-carotene, or placebo. The study was follow-up for five to eight years. Total mortality was higher among the participants who received beta-carotene than among those who did not (The alpha-tocopherol beta-carotene cancer prevention study group, 1994). beta-Carotene supplementation at pharmacologic levels may modestly increase the incidence of lung cancer in cigarette smokers (Albanes et al., 1996).

*Selenium:* Once arsenic was used to treat selenium poisoning in domestic animals. Nowadays, selenium is tried to treat arsenicosis. The dose and duration are important for selenium. Low dose may not produce any effect whereas excessive dose may cause selenium toxicity. In addition, longer duration of treatment is required (up to 14 months). One study shows that supplementation with L-selenomethionine for 6 months shows slight improvement in non-malignant skin lesions in patients, although the improvement was not statistically significant (Verret et al., 2005). Selenium reduces the oxidative damage and oxidative stress related gene expression in rat liver under chronic poisoning of arsenic (Xu et al., 2013).

*Ascorbic acid:* Isolated liver tissues of rat were first loaded with arsenic within the test tube at 37 °C and then treated with ascorbic acid (20 µg/mL) (Saha, 2006). The amount of reduced glutathione in normal liver tissue was  $52.0 \pm 0.2$  µg/g protein. Addition of arsenic to the tissues reduced the amount of

GSH to  $11.5 \pm 0.3$   $\mu\text{g/g}$  protein. But when the arsenic loaded liver tissues were incubated with ascorbic acid, the amount of GSH was  $14.2 \pm 0.1$   $\mu\text{g/g}$  protein (22.6% increase;  $p < 0.001$ ). This study suggests that ascorbic acid increases the GSH level in arsenic-treated rat's liver. However, chronic intake of ascorbic acid may cause stone formation in the urinary tract.

*Alpha-tocopherol:* The serum concentration of alpha-tocopherol in patients with non-malignant skin lesions is not significantly changed from the control (Chung et al., 2006). However, serum concentration does not reflect the tissue concentration. There is 3-fold increased secretion of vitamin E from the skin of chest and back of arsenicosis in comparison to control or arsenic exposed individual (Yousuf et al., 2011). Chest and back skin are important sites of non-malignant skin lesions. A study on the vitamin E levels in the buccal cells of patients shows significantly low concentration in comparison to healthy volunteers. This low level of vitamin E in patients returned toward normal levels following supplementation with vitamin E (200 IU) caplet for 20 weeks (Misbahuddin & Farha, 2013). Supplementation with alpha-tocopherol for 6 months shows slight improvement in non-malignant skin lesions, although the improvement was not statistically significant (Verret et al., 2005).

A study conducted in southwestern Finland shows that alpha-tocopherol had no apparent effect on total mortality, although more deaths from hemorrhagic stroke were observed among the men who received this supplement than among those who did not (The alpha-tocopherol beta carotene cancer prevention study group, 1994).

A significant increase in the levels of protein oxidation, DNA strand breaks, and DNA-protein cross-links was observed in blood, liver, and kidney of rats exposed to arsenic (100 ppm in drinking water) for 30 days (Kadirvel et al., 2007). Co-administration of ascorbic acid and alpha-tocopherol to arsenic-exposed rats

showed a substantial reduction in the levels of arsenic-induced oxidative products of protein and DNA.

Vitamin E ameliorates arsenic-induced toxicities in the liver and kidney of mice (Verma et al., 2004).

*Alpha-lipoic acid:* *In vitro* experiment with small pieces of isolated liver tissue of rats incubated first in presence of arsenic and then with different concentrations of  $\alpha$ -lipoic acid during the second incubation showed decreased amount of arsenic and malondialdehyde as well as increased the reduced glutathione level in dose dependent manner (Noor-E-Tabassum, 2006). These results suggest that  $\alpha$ -lipoic acid remove arsenic from arsenic-loaded isolated liver tissues of rat.

*Zinc:* Rats were initially allowed to drink high concentration (400  $\mu\text{g/kg/day}$ ) of arsenic for two months followed by a period of cessation (one month) (Kamaluddin & Misbahuddin, 2006). Then the effect of zinc (2  $\text{mg/kg/day}$ ) in the removal of accumulated arsenic from different tissues (liver, kidneys, spleen and lungs) was examined. In arsenic-treated rats, the mean ( $\pm$  SD) amounts of total arsenic in liver, kidneys, spleen and lungs were  $12.3 \pm 0.7$ ,  $20.5 \pm 1.0$ ,  $31.4 \pm 1.0$  and  $25.6 \pm 1.1$   $\mu\text{g/g}$  of tissues respectively. Administration of zinc to arsenic-treated rats reduced the arsenic concentrations of those tissues to 7.8, 10.7, 23.0 and 14.0  $\mu\text{g/g}$  of tissues. This *in vivo* study suggests that zinc removes the accumulated arsenic from different tissues significantly ( $p < 0.001$ ).

Chronic intake of arsenic led to several folds higher secretion of zinc both in arsenicosis and arsenic-exposed controls than the healthy controls (Yousuf et al., 2011). The amount of zinc from the abdomen was similar in arsenicosis and arsenic exposed controls. Arsenicosis had higher level of zinc than that of arsenic-exposed controls in chest ( $15.6 \pm 6.9$  vs.  $12.1 \pm 9.0$   $\mu\text{g/inch}^2/24$  hours)



and back ( $12.6 \pm 5.4$  vs.  $9.0 \pm 6.0$   $\mu\text{g}/\text{inch}^2/24$  hours). The differences between the patients and arsenic-exposed controls were not statistically significant. The secretion of one molecule of arsenic was accompanied by secretion of two molecules of zinc.

Zinc consumed during the perinatal period of pregnancy can ameliorate the possible toxicities of arsenic exposure in the offspring by acting as an ameliorative supplement (Ahmad et al., 2013).

*Folic acid:* Folic acid plays an important role in the biotransformation of arsenic. Arsenic is methylation to MMA and DMA by a folate-dependent process. People having polymorphisms in certain genes involved in folate metabolism excrete low amount of DMA in urine, which may influence susceptibility to arsenic toxicity. A double-blind study in a population with low plasma folate observed that after 12 weeks of folic acid supplementation, the proportion of total urinary arsenic excreted as DMA increased and blood arsenic concentration decreased (Kile & Ronnenberg, 2008).

A study conducted on arsenic-treated rats (700  $\mu\text{g}/\text{day}$  by gavage for 28 days) showed accumulation of arsenic in liver, kidney, heart, lung and skin which was significantly lowered ( $p < 0.05$ ) by both the folic acid and tetrahydrofolate (Rahman & Misbahuddin, 2010). Folic acid was found to be more efficacious compared to tetrahydrofolate.

Two hundred arsenic exposed adults with low plasma folic acid level showed significantly increased excretion of DMA in urine in comparison to control following folic acid supplementation of 0.4 mg/day for 12 weeks (Gamble et al., 2006). Folic acid can cause adverse-effects like depression, nausea, vomiting and skin rashes. It is, therefore, important to determine the correct dose and course length of folic acid in order to avoid adverse effects.

There role of folic acid in the treatment of arsenicosis is not yet studied.

*Garlic:* Twenty patients of mild to moderate degree of arsenical palmer keratosis were treated with garlic oil in soft capsule (10 mg) daily orally for 12 weeks (Misbahuddin et al., 2013). The mean ( $\pm$ SD) clinical scoring of patients before treatment was  $102.8 \pm 19.0$ . It was reduced to  $36.0 \pm 8.7$  after completion of treatment (65% reduction). The mean amounts of total arsenic in nail of patients and arsenic exposed controls were 13 to 14-fold higher in comparison to healthy volunteers. Treatment with garlic oil reduced about 50% of the total arsenic accumulated in nails. Common adverse effects were garlic smell and gastric irritation. Oral administration of garlic oil improves symptom of arsenical palmer keratosis with reduction in body arsenic load.

*Spirulina:* Spirulina is blue-green algae. It is considered as superfood. Spirulina is available in the market for the treatment of several diseases. A placebo-controlled double-blind study was conducted to evaluate effectiveness of spirulina extract (250 mg) plus zinc (2 mg) twice daily for 16 weeks in the treatment of 24 cases of arsenicosis (Misbahuddin et al., 2006). The concentrations of total arsenic in water (without filtration) of placebo-and spirulina extract plus zinc-treated groups were  $150.1 \pm 18.3$  and  $161.7 \pm 23.9$  mg/L, respectively. Intake of these high concentrations of arsenic lead to increased excretion of arsenic in urine ( $72.1 \pm 14.5$  mg/L in placebo-treated group and  $78.4 \pm 19.1$ mg/L in spirulina plus zinc-treated group). After 2 weeks of using filtered water, there were significant reduction of both arsenic intake through water and urinary arsenic excretion ( $8.3 \pm 3.6$  mg/L and  $18.4 \pm 7.3$  mg/L in placebo group;  $9.7 \pm 5.4$  mg/L and  $21.6 \pm 5.8$  mg/L) in spirulina extract plus zinc-treated group. There was a sharp increase in urinary excretion of arsenic ( $138 \pm 43.6$  mg/L) at 4 weeks following spirulina plus zinc administration and the effect was continued for another 2 weeks. Spirulina extract plus zinc

removed 47.1% arsenic from scalp hair. Spirulina extract had no major adverse effect that required physician's attention. In spirulina extract plus zinc-treated group, the clinical scores for keratosis before and after treatment was statistically significant ( $p < 0.05$ ). Results show that spirulina extract plus zinc may be useful for the treatment of arsenicosis with keratosis.

*Corn:* Water extract of corn reduced the amount of arsenic in different tissues of rat after exposure to arsenic (700  $\mu\text{g}/\text{rat}/\text{day}$ ) orally for 15 days (Chowdhury et al., 2009). Maximum reduction of arsenic occurred in liver (69.1%), kidneys (65.0%), lungs (63.5%), heart (57.6%) and skin (69.3%) and elevation of reduced glutathione level in all tissues (17.0% in liver, 46.7% in lung, 32.7% in heart and 55.4% in skin) except kidneys. This study suggests that corn extracts might protect rats from accumulation of arsenic in different tissues and oxidative stress, which is reflected by the increasing reduced glutathione concentration in those tissues.

*Spinach:* Hexane extract of spinach (1-4%) was effective in the removal of arsenic from arsenic-treated rat (Umar, 2007). Rats were fed arsenic trioxide through Ryle's tube for one month then they were fed on hexane extract of spinach for another one month. Hexane extract of spinach decreased accumulated arsenic from rat liver, spleen, kidney, intestine, lungs and skin significantly. Besides, it reduced the oxidative stress caused by arsenic which was evident by decreased levels of malondialdehyde in the above tissues. Hexane extract decreased both arsenic level and MDA level in rat tissues in dose dependent manner, which was more effective at lower doses.

*Roots of water hyacinth:* Intraperitoneal injection of ethanol extract (dose: 50%) of water hyacinth for two days showed maximum arsenic lowering effect from different tissues of arsenic-treated rats (administered orally 500  $\mu\text{g}/\text{rat}/\text{day}$  for 7 days) (Quayum, 2007). Besides, it reduced the oxidative stress caused by

arsenic, which was evident by decreased levels of malondialdehyde in tissues.

*Curcumin:* Curcumin is obtained from turmeric (popular South Asian spice) has its antioxidant and antimutagenic activity (Biswas et al., 2010). Blood samples taken from arsenicosis showed notable DNA damage and depleted antioxidant activity. Following dosage with curcumin capsules for three months, the DNA damage was reduced, ROS generation and lipid peroxidation was suppressed, and the antioxidant activity of blood plasma was raised. Arsenic-induced oxidative stress, apoptosis and alterations in testicular steroidogenesis and spermatogenesis in Wistar rats are ameliorated by curcumin (Khana et al., 2013).

*Nigella sativa (Kala jeera):* The oral administration of *N. sativa* oil (500 mg) capsules twice daily for 8 weeks is affective for the clinical improvement of palmar arsenical keratosis which is reflected by decreasing total arsenic load in nail as well as mean clinical scoring (Basher et al., 2014). Exact mechanism of effect is not known. However, there is protective effect of thymoquinone of *Nigella sativa* origin against arsenic-induced testicular toxicity in rats (Fouad et al., 2014).

*Methionine:* Arsenic consumed through drinking water may be quickly excreted from the body through methylation in the body through mostly urine. This methylation reaction needs methyl donors coming from food sources and it competes with normal metabolic processes. If body has enough supply of certain nutrient components like methionine, the toxic effects of arsenic are much reduced.

*Green and black tea:* Both teas afford efficient reduction of As<sup>III</sup>-induced DNA damage in human lymphocytes (Sinha et al., 2007). It also quenched the excessive production of reactive oxygen species by arsenic, reduced the

elevated levels of lipid peroxidation, and increased the activity of antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase). Furthermore, tea enhanced recovery of DNA damage, which was indicative of repair as confirmed by unscheduled DNA synthesis and pronounced expression of DNA repair enzyme poly (ADP-ribose) polymerase.

*Probiotics:* After 12 weeks supplementation with one capsule of probiotics (*Lactobacilli bugaicus* and *Bifidobacterium*), both *E. coli* count and stool arsenic level were significantly increased in patients (Rashid et al., 2014).

*Co-administration:* A study using rats showed that oral administration of zinc (1 mg/kg body weight/day) for 1 month is effective in the prevention of arsenic accumulation in different tissues such as spleen, lungs, kidneys, intestine and skin. But simultaneous administration of zinc and arsenic increased the accumulation of arsenic in different tissues particularly kidneys and spleen (Misbahuddin & Kamaluddin, 2002). The cause of which is not known but there may be enhanced absorption of arsenic by zinc. Simultaneous administration of selenium and arsenic enhanced the accumulation of arsenic in different tissues of rat (Nasir et al., 2002). Ascorbic acid enhances arsenic trioxide-induced cytotoxicity in multiple myeloma cells (Grad et al., 2001).

In case of spirulina, it takes months whereas in case of vitamin E, it takes 14 months treatment. This prolong treatment influences treatment cost and adherence. In addition, stoppage of drug intake reappears the symptom. Intake of beta-carotene or retinol may cause lung cancer. Simultaneous administration of zinc, selenium or manganese with arsenic may enhance the accumulation of arsenic in tissues.

## 10.2 Peripheral Vascular Disease

Peripheral vascular disease associated with gangrene is treated with drugs like pentoxifyllin or calcium channel blockers with limited effect. Most of these patients need surgical amputation.

## 10.3 Peripheral Neuropathy

Tricyclic antidepressants such as amitriptyline may have utility in relieving painful dyesthesias of arsenical peripheral neuropathy (Wilner & Low, 1993).

## 10.4 Respiratory Symptoms

In chronic bronchitis with or without obstruction, it is extremely important that bronchial irritation be reduced to a minimum. Smoking habits and dusty and smoke-laden atmospheres are to be avoided, and respiratory infection should be treated promptly. Bronchodilators have a limited role in interstitial lung diseases.

## 10.5 Treatment Options for Bowen's Disease

Several points should be considered before choosing the treatment option of Bowen's disease. These are the size, number and site of lesion and cost. The treatment options of Bowen's disease are: a) drug therapy, b) cryotherapy, c) curettage and cautery, d) laser therapy, e) photodynamic therapy, f) radiation, and g) excision. Most of these therapies have the risk of recurrence. Follow-up after each therapy for at least 6 to 12 months are required to evaluate the recurrence. These appear to have generally similar efficacy and recurrence rates with no single therapy being superior for all clinical situations.

Drug therapy includes acitretin, 5-fluorouracil, imiquimod and diclofenac. Acitretin is given orally whereas 5-fluorouracil, imiquimod and diclofenac are applied topically.

*Acitretin:* Daily treatment of acitretin (1 mg/kg) orally for 10 months cures Bowen's disease (Yerebaken et al., 2002). Apparent improvement was visible after three months of treatment. The effectiveness of this drug was found only in one patient. Another patient did not show any effectiveness due to discontinuation of the drug. It is readily absorbed from the gut and widely distributed with a plasma half-life of 2 days. It may cause nausea, itching, headache, dry, red or flaky skin, dry or red eyes, dry or chapped lips, swollen lips, dry mouth, thirst, hair loss, depression or acne. There may be the possibility of severe birth defects and should not be used by pregnant women or women planning to get pregnant within 3 years following the use of acitretin.

Patient may be treated with acitretin 25 mg daily (Watson & Creamer, 2003). At this dose the patient may respond well with considerable improvement in lesions, many of which have cleared completely.

*5-Fluorouracil:* 5-Fluorouracil is a pyrimidine analogue that is used topically to the affected site as 3% cream once or twice daily for 9 weeks in the treatment of cancer (Sturm, 1979). It may cause the skin to become red and inflamed before it gets better. It acts by interfering DNA synthesis via inhibition of thymidylate synthetase and subsequently cell proliferation. The common adverse effect is irritation with erosions and ulcerations that may last several weeks. The effectiveness of treatment is increased (up to 96%) when 5-FU is combined with other therapeutic approaches like pretreatment with erbium:YAG laser, cryotherapy, imiquimod and acitretin (Khandpur & Sharma, 2003).

*Imiquimod:* Imiquimod, an immunomodulator, is applied to the affected skin regularly as cream (5%) once daily for 16 weeks in the treatment of Bowen's disease (Rosen et al., 2007). It may cause the skin to become red and inflamed before it gets better. It is usually recommended for lesion of larger-diameter and in leg. Follow-up study shows that recurrence developed after 19 months.

*Diclofenac:* Diclofenac sodium is used as an analgesic. There is a report on two cases of Bowen's disease treated with 3% diclofenac gel twice daily for 80 to 90 days with no residual disease clinically and histologically (Dawe et al., 2005). The treatment is well-tolerated with mild inflammation after 6 weeks. There may be mild adverse effects like itching and dryness.

*Cryotherapy:* Liquid nitrogen is sprayed onto the affected skin to freeze it. This procedure of freeze-thaw cycles are done twice. Each freeze cycle is being maintained for 5-10 second after the formation of an ice ball to the intended margin. The procedure may be painful and the skin may remain a bit uncomfortable for a few days. The treated area may blister and weep. The patch will scab over afterwards and usually fall off within a few weeks, removing the affected skin.

*Curettage and cautery:* The affected area of skin is scraped away under local anesthetic and heat or electricity is used to stop any bleeding, leaving the area to scab over and heal after a few weeks. Curettage and cautery are superior to cryotherapy in the treatment of Bowen's disease, especially for lesions on the lower leg (Ahmed et al., 2000). The abnormal skin is cut out and stitches may be needed afterwards. It is not the best option if the patch is large or if there are several patches.

*Laser therapy:* Complete response of Bowen's disease of the digits by CO<sub>2</sub> laser with no recurrence in the 0.5 to 7.7 years follow-up was published in some



studies with good functional and cosmetic outcome.

*Photodynamic therapy:* A light-sensitive cream is applied to the affected skin and a laser is directed onto the skin four to six hours later, to destroy the abnormal cells. The treatment session lasts about 20-45 minutes. A dressing covers the area afterwards, to protect it from light. The most commonly used photosensitizers are 5-aminolevulinic acid or methyl aminolevulinate that are used topically. Various illumination sources, wavelengths of light, and dosing schedules have been used. Photodynamic therapy is well-suited for large lesions, multiple lesions, and poor-healing sites. The adverse effects are burning and stinging. There may be rarely observed adverse effects like erosions, ulceration, and hyperpigmentation hypopigmentation.

*Radiotherapy:* X-ray or grenz-ray radiation therapy may be given for poor surgical candidates or patients with multiple lesions. It should be avoided for lower extremity lesions due to impaired healing.

*Excision:* The surgical excision of Bowen's disease is one of the standard treatments especially for small and single, digital and perianal Bowen's disease (Neubert & Lehmann, 2008). A study conducted on perianal Bowen's disease shows that recurrence rate for wide excision, local excision and laser therapy is 23%, 53% and 80% respectively (treatment with radiotherapy was not included) (Marchesa et al., 1997).

## 10.6 Treatment of Skin Cancer

*Beta-carotene:* Individual who selects diet high in beta-carotene has a lower incidence of squamous cell carcinoma and basal cell carcinoma (Kune et al., 1992; Hsueh et al., 1997).

## 10.7 Other Cancers

Cancer in lungs, urinary bladder or liver is not very rare. In this case, excision of bladder cancer due to chronic arsenicosis can be curative. In advanced cases of these cancers and in cases of internal cancers, the treatment options are meager.

Surgical intervention in mild-to-moderate keratotic papules or nodules has not been widely tried. Those lesions with sudden increase in size, cracks, and bleeding; and those of Bowen's disease, basal cell carcinoma, squamous cell carcinoma need to be surgically excised at the earliest opportunity.

## References

- [1] Aaseth, J. (1983). Recent advances in the therapy of metal poisoning with chelating agents. *Human Toxicology*, 2, 257-272.
- [2] Ahmad, M., Wadaan, M. A. M., Farooq, M., Daghestani, M. H., & Sami, A. S. (2013). Effectiveness of zinc in modulating perinatal effects of arsenic on the teratological effects in mice offspring. *Biological Research*, 46(2), 131-138.
- [3] Ahmed, I., Berth-Jones, J., Charles-Homes, S., O'Callaghan, C. J., & Ilchshyn, A. (2000). Comparison of cryotherapy with curettage in the treatment of Bowen's disease: A prospective study. *British Journal of Dermatology*, 143(4), 759-766.
- [4] Albanes, D., Heinonen, O. P., Taylor, P. R., Virtamo, J., Edwards, B. K., Rautalahti, M., Hartman, A. M., Palmgren, J., Freedman, L. S., Haapakoski, J., Barrett, M. J., Pietinen, P., Malila, N., Tala, E., Liippo, K., Salomaa, E. R., Tangrea, J. A., Teppo, L., Askin, F. B., Taskinen, E., Erozan, Y., Greenwald, P., & Huttunen, J. K. (1996). Alpha-tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. *Journal of National Cancer Institute*, 6, 88(21), 1560-1570.
- [5] Bashar, T., Misbahuddin, M., & Hossain, M. A. (2014). A double-blind, randomized, placebo-control trial to evaluate the effect of *Nigella sativa* on palmer arsenical keratosis patients. *Bangladesh Journal of Pharmacology*, 9, 15-21.

- [6] Biswas, J., Sinha, D., Mukherjee, S., Roy, S., Siddiqi, M., & Roy, M. (2010). Curcumin protects DNA damage in a chronically arsenic – exposed population of West Bengal. *Human & Experimental Toxicology*, 29, 513-524.
- [7] Chowdhury, N. J. A., Misbahuddin, M., & Rahman, M. S. (2009). Corn extracts lower tissue arsenic level in rat. *Bangladesh Medical Research Council Bulletin*, 35(1), 21-25.
- [8] Chung, J. S., Haque, R., Guha Mazumder, D. N., Moore, L. E., Ghosh, N., Samanta, S., Mitra, S., Hira-Smith, M. M., von Ehrenstein, O., Basu, A., Liaw, J., & Smith, A. H. (2006). Blood concentrations of methionine, selenium, beta-carotene, and other micronutrients in a case-control study of arsenic-induced skin lesions in West Bengal, India. *Environmental Research*, 101(2): 230-237.
- [9] Dawe, S. A., Salisbury, J. R., & Higgins, E. (2005). Two cases of Bowen's disease successfully treated topically with 3% diclofenac in 2.5% hyaluronan gel. *Clinical & Experimental Dermatology*, 30, 712-713.
- [10] Dina, A. N., & Misbahuddin, M. (2010). Randomized double-blind trial to evaluate the effectiveness of topical administration of propylene glycol in arsenical palmer keratosis. *Bangladesh Journal of Pharmacology*, 5, 98-102.
- [11] Ferdoush, J., & Misbahuddin, M. (2014). Effect of ethanol extract of leaves of *Azadirachta indica* on palmar arsenical keratosis: A single-blind trial. *Bangladesh Journal of Pharmacology*, 9(3), 279-283.
- [12] Fouad, A. A., Albuali, W. H., & Jresat, I. (2014). Protective effect of thymoquinone against arsenic-induced testicular toxicity in rats. *International Journal of Medical, Pharmaceutical Science & Engineering*, 8(2), 46-49.
- [13] Gamble, M. V., Liu, X., Ahsan, H., Pilsner, J. R., Ilievski, V., Slavkovich, V., Parvez, F., Chen, Y., Levy, D., Factor-Litvak, P., & Graziano, J. H. (2006). Folate and arsenic metabolism: A double-blind, placebo-controlled folic acid-supplementation trial in Bangladesh. *American Journal of Clinical Nutrition*, 84, 1093-1101.
- [14] Ghosh, C. K., Datta, B. K., Biswas, S., Maji, C., Sarkar, S., Mandal, T. K., Majumder, D., & Chakraborty A. K. (2011). Chronic arsenicosis of cattle in West Bengal and its possible mitigation by sodium thiosulfate. *Toxicology International*, 18(2), 137-139.

- [15] Grad, J. M., Bahlis, N. J., Reis, I., Oshiro, M. M., Dalton, W. S., & Boise, L. H. (2001). Ascorbic acid enhances arsenic trioxide-induced cytotoxicity in multiple myeloma cells. *Blood*, 98(3), 805-813.
- [16] Guha Mazumder, D. N., Ghoshal, U. C., Saha, J., Santra, A., De, B. K., Chatterjee, A., Dutta, S., Angel, C. R., & Centeno, J. A. (1998). Randomized placebo-controlled trial of 2, 3-dimercaptosuccinic acid in therapy of chronic arsenicosis due to drinking arsenic-contaminated subsoil water. *Clinical Toxicology*, 36(7): 683-690.
- [17] Guha Mazumder, D. N., De, B. K., Santra, A., Ghosh, N., Das, S., Lahiri, S., & Das, T. (2001). Randomized placebo-controlled trial of 2, 3-dimercapto-1-propanesulfonate (DMPS) in therapy of chronic arsenicosis due to drinking arsenic-contaminated water. *Journal of Toxicology & Clinical Toxicology*, 39(7): 665-674.
- [18] Hall, A. F. (1946). Arsenical keratosis disappearing with vitamin A therapy. *Archives of Dermatology Syph*, 53, 154.
- [19] Hsueh, Y. M., Chiou, H. Y., Huang, Y. L., Wu, W. L., Huang, C. C., Yang, M. H., & Chen, C. J. (1997). Serum beta-carotene level, arsenic methylation capability, and incidence of skin cancer. *Cancer Epidemiology, Biomarkers & Prevention*, 6(8), 589-596.
- [20] Islam, A. Z. M. M., Misbahuddin, M., Sikdar, S., Biswas, A. K., Islam, Z., Hadiuzzaman, Khandker S, Iftakher-Al-Mahmud, & Ahmad, S. A. (2007). Randomized controlled trial to evaluate the effectiveness of topical use of salicylic acid for treatment of keratosis in arsenicosis patients. In: Applied research on arsenic in Bangladesh. Misbahuddin, M. (ed). Dhaka, WHO and Government of Bangladesh, 92-100.
- [21] Kadirvel, R., Sundaram, K., Mani, S., Samuel, S., Elango, N., & Panneerselvam, C. (2007). Supplementation of ascorbic acid and alpha-tocopherol prevents arsenic-induced protein oxidation and DNA damage induced by arsenic in rats. *Human & Experimental Toxicology*, 26(12), 939-946.
- [22] Kamaluddin, M., & Misbahuddin, M. (2006). Zinc supplement reduces tissue arsenic concentration in rats. *Bangladesh Medical Research Council Bulletin*, 32, 87-91.
- [23] Khana, S., Telangb, A. G., & Malika, J. K. (2013). Arsenic-induced oxidative

stress, apoptosis and alterations in testicular steroidogenesis and spermatogenesis in wistar rats: Ameliorative effect of curcumin. *Wudpecker Journal of Pharmacy & Pharmacology*, 2(3), 33-48.

- [24] Khandpur, S., & Sharma, V. K. (2003). Successful treatment of multiple pre-malignant and malignant lesions in arsenical keratosis with a combination of acitretin and intralesional 5-fluorouracil. *Journal of Dermatology*, 30, 730-734.
- [25] Kile, M. L. & Ronnenberg, A. G. (2008). Can folate intake reduce arsenic toxicity? *Nutrition Reviews*, 66(6), 349-353.
- [26] Kune, G. A., Bannerman, S., Field, B., Watson, L. F., Cleland, H., Merenstein, D., & Vitetta, L. (1992). Diet, alcohol, smoking, serum beta-carotene, and vitamin A in male nonmelanocytic skin cancer patients and controls. *Nutrition & Cancer*, 18, 237-244.
- [27] Marchesa, P., Fazio, V. W, Oliart, S, et al. (1997). Perianal Bowen's disease: A clinicopathologica study of 47 patients. *Diseases of the Colon & Rectum*, 40: 1286-1293.
- [28] Misbahuddin, M., & Farha, N. (2013). Vitamin E levels in buccal cells of arsenicosis patients following vitamin E supplementation. *Bangladesh Journal of Pharmacology*, 8, 236-241.
- [29] Misbahuddin, M., & Kamaluddin, M. (2002). Simultaneous administration of zinc and arsenic enhances accumulation in tissues. *BMJ (rapid response)*, 14.
- [30] Misbahuddin, M., Bashar, T., & Hossain, M. A. (2013). Effectiveness of garlic oil in the treatment of arsenical palmer keratosis. *Bangladesh Journal of Pharmacology*, 8, 22-27.
- [31] Misbahuddin, M., Islam, A. Z. M. M., Khandker, S., Ifthaker-Al-Mahmud, Islam, N., & Anjumanara, (2006). Efficacy of spirulina extract plus zinc in patients of chronic arsenic poisoning: A randomized placebo-controlled study. *Clinical Toxicology (Philadelphia)*, 44(2), 135-141.
- [32] Nasir, M., Misbahuddin, M., & Ali, S. M. K. (2002). Selenium intervention in reducing arsenic levels in different tissues. In: Bangladesh Environment 2002. Proceedings of the 2nd International Conference on Bangladesh Environment. Ahmed, M. F., Tanveer, S. A., & Badruzzaman, A. B. M. (eds). ICBEN-2002, Dhaka, Bangladesh, pp 343-52.

- [33] Neubert, T., & Lehmann, P. (2008). Bowen's disease: A review of newer treatment. *Therapeutics & Clinical Risk Management*, 4(5), 1085-1095
- [34] Noor-E-Tabassum, (2006). Effect of  $\alpha$ -lipoic acid on the removal of arsenic from arsenic-loaded isolated liver tissues of rat. *Bangladesh Journal of Pharmacology*, 1, 27-32.
- [35] Quayum, S. L. (2007). Effect of water hyacinth root extract on arsenic level in different organs of arsenic-treated rat. *Bangladesh Journal of Pharmacology*, 2, 73-80.
- [36] Rahman, M. F., & Misbahuddin, M. (2010). Effect of folic acid and tetrahydrofolate on tissue arsenic level in rat. *Bangladesh Journal of Pharmacology*, 5, 25-29.
- [37] Rashid, N., Misbahuddin, M., Choudhry, Z. K., Saleh, A. A., & Sattar, N. I. (2014). The colony count of *Escherichia coli* in the stool of palmar arsenical keratosis following probiotics supplementation. *Bangladesh Journal of Pharmacology*, 9(2), 176-181.
- [38] Ravaut, P. (1920). Internal treatment of skin disease. *Presse Medicine*, 28, 73.
- [39] Rosen, T., Harting, M., & Gibson, M. (2007). Treatment of Bowen's disease with topical 5% imiquimod cream: Retrospective study. *Dermatological Surgery*, 33(4), 427.
- [40] Saha, B. (2006). Effect of ascorbic acid on reduced glutathione level in arsenic-loaded isolated liver tissues of rat. *Bangladesh Journal of Pharmacology*, 1, 68-71.
- [41] Sinha, D., Dey, S., Bhattacharya, R. K., & Roy, M. (2007). *In vitro* mitigation of arsenic toxicity by tea polyphenols in human lymphocytes. *Journal of Environmental Pathology, Toxicology and Oncology*, 26, 207-220.
- [42] Son, S. B., Song, H. J., & Son, S. W. (2008). Successful treatment of palmoplantar arsenical keratosis with a combination of keratolytics and low-dose acitretin. *Clinical and Experimental Dermatology*, 33(2), 202-204.
- [43] Sturm, H. M. (1979). Bowen's disease and 5-fluorouracil. *Journal of American Academy of Dermatology*, 1(6), 513-522.
- [44] The alpha-tocopherol, beta-carotene cancer prevention study group. (1994). The

effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers. *New England Journal of Medicine*, 330, 1029-1035.

- [45] Umar, B. U. (2007). Effect of hexane extract of spinach in the removal of arsenic from rat. *Bangladesh Journal of Pharmacology*, 2, 27-34.
- [46] Verma, R. J., Vasu, A., & Saiyed, A. A. (2004). Arsenic toxicity in mice and its possible amelioration. *Journal of Environmental Science (China)*, 16(3), 447-453.
- [47] Verret, W. J., Chen, Y., Ahmed, A., Islam, T., Parvez, F., Kibriya, M. G., Graziano, J. H., & Ahsan, H. (2005). A randomized, double-blind placebo-controlled trial evaluating the effects of vitamin E and selenium on arsenic-induced skin lesions in Bangladesh. *Journal of Occupational & Environmental Medicine*, 47(10), 1026-1035.
- [48] Watson, K., & Creamer, D. (2003). Arsenic-induced keratoses and Bowen's disease. *Clinical and Experimental Dermatology*, 29(1), 46-48.
- [49] Wilner, C., & Low, P. A. (1993). Pharmacological approaches to neuropathic pain In: *Peripheral neuropathy*. Dyck, P. J (ed). Philadelphia, WB Saunders, pp 1709-1720.
- [50] Xu, Z., Wang, Z., Li, J. J., Chen, C., Zhang, P. C., Dong, L., & Wang, Z. L. (2013). Protective effects of selenium on oxidative damage and oxidative stress related gene expression in rat liver under chronic poisoning of arsenic. *Food & Chemical Toxicology*. 58, 1-7.
- [51] Yerebaken, O., Ermis, O., Yilmaz, E., & Basaran, E. (2002). Treatment of arsenic keratosis and Bowen's disease with acitretin. *International Journal of Dermatology*, 41, 84-87.
- [52] Yousuf, A. K. M., Misbahuddin, M., & Rahman, M. S. (2011). Secretion of arsenic, cholesterol, vitamin E, and zinc from the site of arsenical melanosis and leucomelanosis in skin. *Clinical Toxicology*, 49, 374-378.

