IS STOPPING *SCHISTOSOMA HAEMATOBIUM*-ASSOCIATED BLADDER CANCER A FEASIBLE GOAL?

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At present schistosomiasis is endemic in 78 countries affecting more than 260 million people. Schistosomiasis haematobia alone affects more than 112 million people. Bladder cancer is an important sequela of this infection. In low-resource countries, where this disease is endemic, individuals diagnosed with bladder cancer have very limited access to treatment and death is almost a certainty. Mass treatment with praziquantel is an easy, safe and inexpensive treatment that could save the lives of thousands and reduce the morbidity of millions.

Schistosomiasis: Facts and figures

Schistosomiasis is an ancient scourge of mankind, depicted in papyri from Pharaonic Egypt and found in human remains over 2,000 years old in China. Human schistosomiasis is caused by six species: *Schistosoma (S.) haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum*, *S. guineensis* and *S. mekongi*. A further species *S. malayensis* has been identified that infects humans in a limited way in Malaysia *(1)*.

Schistosomiasis was originally called bilharziasis in homage to Theodor Bilharz, a young German pathologist who first described the disease and its association with *Schistosoma* worms whilst working in Cairo, Egypt. Blood-dwelling *Trematoda* (phylum Platyhelminthes) of the genus *Schistosoma* cause this chronic and debilitating disease *(2)*. Schistosomes present a heteroxenic life cycle, requiring as secondary host an invertebrate freshwater snail. Geographic distribution and maintenance of human infection depends on the presence of a suitable snail host. Adult worms are sexually distinct, a characteristic that separates them from other flukes that are hermaphrodites. Males present a ventral infolding from the ventral sucker to the posterior end forming the gynecophoric canal, where females are kept during copulation (copulatory groove). The *Schistosoma* life cycle also differs from that of other flatworms by the infecting process of the definitive host: the penetration of cercariae through the skin. Of the *Schistosoma* species pathogenic to humans, only *Schistosoma haematobium* causes urinary schistosomiasis *(3)*. Snails of the genus *Bulinus* are the principle intermediate hosts for *S. haematobium*. Animals may play a role in *S. haematobium* infections as they may hybridize with closely related zoonotic *Schistosoma spp.* such as *S. bovis (4)*.

Since 1989, schistosomiasis has been endemic in 76 countries *(5)*. A recent World Health Organization (WHO) report declared schistosomiasis endemic in 78 countries *(6, 7)*. The estimated total number of people requiring treatment for schistosomiasis in 2013 was 261,008,019, of whom 121,170,936 (46.4%) were school-age children (5–14 years of age) *(7)*.

S. haematobium is endemic in 53 countries in the Middle East and most of the African continent, including the islands of Madagascar and Mauritius. Due to successful eradication programmes, the infection is no longer of public health significance in Egypt, Lebanon, Oman, Syria, Tunisia and Turkey because transmission is low or nonexistent. A disputed and ill-defined focus exists in India that requires further confirmation *(2)*. After more than 50 years in which no more autochthonous cases of schistosomiasis were recorded in Europe, *S. haemaatobium* infection has recently emerged in Corsica *(8)*.

Schistosomiasis-associated bladder cancer

Squamous cell carcinoma of the bladder (SCC) is a malignant, poorly differentiated neoplasm. SCC is the common form of bladder cancer in rural Africa where *S. haematobium* is prevalent *(9, 10)*. By contrast, the majority of bladder cancer in developing countries and regions not endemic for urogenital schistosomiasis is transitional cell carcinoma (TCC), which arises from the transitional epithelium lining of the bladder. The parasite eggs trapped in the bladder wall release antigens and other metabolites (presumably evolved to expedite egress to the urine, and hence to the external environment). The phenomenon leads to haematuria and to chronic inflammation, in turn increasing the risk of SCC of the bladder. The epidemiological association between SCC of the bladder with schistosomiasis haematobia is based both on case control studies and on the correlation of bladder cancer incidence with prevalence of *S. haematobium* infection within diverse geographic areas. The incidence of urogenital schistosomiasis-associated SCC is estimated at 3–4 cases per 100,000 per year *(11)*. Schistosomiasis haematobia is a chronic infection. The adult, egg-producing schistosomes live for many years, re-infections occur frequently, and schistosomiasis-associated bladder SCC appears relatively early, often by the mid-decades of life (TCC usually presents in the later decades of life). In a recent monograph, the International Agency for Research on Cancer (IARC) confirmed that chronic infection with *S. haematobium* causes cancer of the urinary bladder *(12)*.

Our group has been working on the identification of parasite-derived compounds that might be implicated in the carcinogenesis of *S. haematobium*. The majority of these compounds are catechol estrogens. The genotoxic effects of these estrogen metabolites might be attributed to oxidation of catechol estrogens to quinones, followed by redox cycling and the formation of reactive oxygen species that in turn react with DNA *(13)*. Given the context of the unarguable link between *S. haematobium* infection and bladder cancer, the presence of putative carcinogenic molecules in *S. haematobium* eggs hopefully may have practical consequences for new approaches to disease control *(14, 15)*. The metabolism of estrogens and the production of depurinating estrogen–DNA adducts can be implicated in a pathway underlying *S. haematobium*-promoted host cell DNA damage, leading eventually to cell transformation. The carcinogenic effect of this estrogen–DNA adduct mediated pathway could explain the link between chronic schistosomiasis haematobia and SCC of the bladder. We anticipate that these findings will contribute to understanding how schistosomiasis haematobia leads to SCC of the bladder *(13)*.

Treatment cost of bladder cancer

Although costs of medical care for bladder cancer have been investigated extensively, patient time costs associated with cancer care have rarely been estimated systematically. Yabroff and colleagues *(16)* identified 763,527 patients in the United States with cancer from 1995 to 2001. Net time-cost estimates for the initial phase of care were applied to national estimates of the numbers of new cancers in 2005 to obtain national time-costs for the initial phase of care. According to these authors in 2005, patient time-costs for the initial phase of care were US$ 2.3 billion *(16)*.

In another example, the diagnosis and treatment of bladder cancer represents a significant financial burden to the population in the United States. Therapeutic advances in bladder cancer care have come at a high cost to payers, providers and patients. In this study Noyes et al *(17)* describe the principles of cost-effectiveness evaluation in health care and provide recommendations for a more economical use of resources in bladder cancer care. Although several studies have demonstrated that bladder cancer is a common disease associated with substantial economic burden for patients and society, the evidence supporting the cost-effectiveness of many interventions in bladder cancer care is limited and of insufficient quality. In addition, very little is known about quality of life, the preferred outcome measure for economic evaluations, associated with bladder cancer states and treatments. Moreover, current clinical guidelines for bladder cancer care do not incorporate economic factors when evaluating clinical pathways *(17)*.

In Canada, bladder cancer is the most costly malignancy to treat per patient. Treatment options for bladder cancer are immediate cystectomy and conservative therapy with intravesical Bacillus Calmette-Guerin (BCG). The corresponding mean per-patient discounted lifetime costs in 2005 were Can$ 37,600 and Can$ 42,400, respectively *(18)*. In 2006 the annual cost of care for all patients with muscle-invasive BC (MIBC) was Can$ 35.72 million, 70% more than the Can$ 21.03 million for patients with non-MIBC. The major cost drivers, regardless of disease stage, were diagnostics/surveillance and complications, accounting for up to 43% and 37% of BC care costs, respectively. Co-morbidity-adjusted incremental annual resource costs per patient with MIBC were more than four times greater than those for patients with non-MIBC, similar to those of OC controls (P = 0.490–0.913), except for inpatient (P = 0.002) and hospice (P <0.001) costs, which were both statistically significantly lower. Annual adjusted incremental Medicare

reimbursements totalled Can$ 36.3 million for non-MIBC and Can$ 96.1 million for MIBC *(19)*.

In 2007, Konety and Allareddy *(20)* identified 6,577 patients in the United States undergoing radical cystectomy for bladder cancer from the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project (1998 to 2002). Of commonly performed urological cancer procedures radical cystectomy is associated with the highest morbidity and mortality. According to these authors the impact of each individual type of complication or a combination of them on various outcome measures, such as mortality, charges and length of stay, is unclear. They attempted to quantify the impact of specific post-cystectomy complications and combinations thereof in terms of mortality, charges and length of stay. Although most patients undergoing cystectomy are older and have multiple comorbidities, the postoperative complications with the most significant impact were those directly related to surgery (primary complications). Secondary complications (cardiac, respiratory, vascular, etc) appear to have less of an impact on most common outcome measures. Median total charges was US$ 41,905 and median length of stay was nine days *(20)*.

Calculations of the treatment costs are limited by the fact that SCC may create different costs to TCC and that costs depend on the current exchange rate of a country's currency with the United States dollar. However, figures allow an approximate estimation of costs SCC would produce in industrialized countries if properly treated according to current standards.

Mass treatment of schistosomiasis and preventive chemotherapy

It has been previously shown that in patients treated with praziquantel, pathological lesions of the urinary tract as shown ultrasonographically will disappear *(21)*. In these patients, the resolution of bladder lesions induced by urinary schistosomiasis resulted in reversibility of urinary tract obstructions one year after treatment with praziquantel *(22 –24)*. Other chronic sequelae like Symmers' fibrosis has been shown to be reversed by praziquantel *(25)*.

We anticipate that the incidence of SCC in endemic areas will decrease to that of non-endemic regions if patients with urinary schistosomiasis are regularly treated from childhood on in spite of constant re-exposure, as it has been demonstrated *(6, 7)*.

The literature provides us with several reports in which mass treatment with praziquantel with the purpose of preventive chemotherapy of schistosomiasis is effective. An intervention study was conducted in Khamir, north of Sana'a Yemen, for control of urinary schistosomiasis using chemotherapy. Prevalence of *S. haematobium* infection 14 months post-intervention fell from 58.9% to 5.8% and frequency of heavy infections fell from 40% to 18.9% *(26)*. Schistosomiasis and soil-transmitted helminthiasis (STH) are among the neglected tropical diseases in Africa. A national control programme for these diseases was initiated in Uganda during March 2003. An annual treatment with praziquantel and albendazole was given to schoolchildren in endemic areas and to adults in selected communities where local prevalence of *S. mansoni* in school children was high. Two rounds of treatment significantly reduced the prevalence of *S. mansoni* infection in school children across three regions in the country from 33.4–49.3% to 9.7–29.6%, and intensity of infection from 105.7–386.8 eggs per gram of faeces (epg) to 11.6–84.1 epg. The proportion of children with heavy *S. mansoni* infection was significantly reduced from 15% (95% CI: 13.4–16.8%) to 2.3% (95% CI: 1.6–3.0%). In this work, the authors showed that annual antihelminthic treatment delivered to school children and to adults at high risk in Uganda can significantly reduce the prevalence and intensity of infection for schistosomiasis and STH, and potentially also significantly reduce levels of environmental transmission of infection *(27)*.

Also, in the case of genital infection with *S. haematobium* it was shown that preventive chemotherapy could be useful. Genital infection with *S. haematobium* is prevalent in sub-Saharan Africa. Epidemiological studies have observed that genital schistosomiasis is associated with an increased chance of HIV infection among women. Ndeffo Mbah and collaborators *(28)* estimated that, in *S. haematobium* high-risk communities, targeted annual treatment of school-age children could reduce HIV prevalence by 20% (95% CI: 12–31%) in Angola, 16% (95% CI: 10–32%) in Kenya, and 6% (95% CI: 3–18%) in Zambia after the first 20 years of intervention *(28)*.

The latest success story in the literature was designed to assess the impact of a decade of biennial mass administration of praziquantel on schistosomiasis in school-age children in Burkina Faso. In 2013, in a national assessment based on 22 sentinel sites, 3,514 schoolchildren aged 7–11 years were checked for *S. haematobium* and *S. mansoni* infection by the examination of urine and stool samples, respectively. Ouedraogo et al *(29)* analyzed the observed prevalence and intensity of infections and compared these with the relevant results of earlier surveys in Burkina Faso. Less than 1% of the children in six regions had heavy *S. haematobium* infections. *S. mansoni* was only detected in two regions. By the mass use of preventive

chemotherapy, Burkina Faso may have eliminated schistosomiasis as a public health problem in eight regions and controlled schistosome-related morbidity in another three regions *(29)*.

On the other hand, the number of people treated for schistosomiasis worldwide in 2013 was 39,485,376. This represents only 12.7% of the population requiring preventive chemotherapy for schistosomiasis globally. Schistosomiasis treatments in 2013 were reported by nine fewer countries than in 2012. In 2013, 160 million praziquantel tablets were delivered to countries in the African region to implement the treatment. This would have been enough to treat about 60 million people. The fact that little more than 26 million people were treated in 2013 suggests that availability of praziquantel was not the only limiting factor for schistosomiasis control in the region *(7)*. Considering that there are at least 112 million people infected with schistosomiasis haematobia *(13, 30, 31, 32)*, and given that 3–4 in 100,000 individuals per year develop bladder cancer (see above), the incidence of SCC attributable to schistosomiasis expected would approximately amount to 5,000 patients per year with bladder cancer caused by *S. haematobium* infection worldwide. The bladder cancer treatment of these patients would cost at least US$ 20 million per year (see above).

In contrast, given that the individual cost per treatment including logistic costs amounts to US$ 0.32 and that a biennial treatment is necessary to prevent serious morbidity due to schistosomiasis, the annual cost per schistosomiasis patient amounts to US$ 0.16 *(33)*. Mass therapy which prevents SCC in schistosomiasis patients would then cost US$ 17.92 million per year and a chronic often incurable disease like SCC would be not only “treated” but safely prevented *(34)*. If only school-age children (46.4%; 5–14 years of age) were targeted the cost would drop to US$ 9.61 million. Affected populations would benefit from the other effects of praziquantel on other complications and sequeleae of schistosomiasis, including renal impairment, increased transmission of HIV, HBV, HTLV and other STDs, sterility, complicated pregnancy, bleeding from esophageal varices, to mention just a few *(35–37)*.

Concluding remarks and future perspectives

Schistosomiasis is a neglected tropical disease which in its early stages is a disease easy to treat and thus to eliminate schistosomiasis-induced SCC. The problem to solve is political rather than medical. More commitment is urgently needed to tackle this disease. Leading policy-makers should be acquainted with this data. Are there simpler and more cost-effective ways of combating cancer than that to eliminate schistosomiasis-induced SCC by preventive praziquantel mass therapy? Preventing schistosomiasis is the best treatment and least expensive way of fighting bladder cancer in endemic areas. ■

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