Cancer and tropical disease therapeutic research: A call for deeper and wider ties

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Citation

Y Meunier. *Cancer and tropical disease therapeutic research: A call for deeper and wider ties*. The Internet Journal of Tropical Medicine. 2006 Volume 4 Number 1.

Abstract

After discussing the links between cancer and tropical diseases, this article identifies some obstacles to closer and broader co-operation between cancer and tropical disease research, shows some common therapeutic uses and contributions and makes general recommendations on how to improve the quantity and quality of work in both specialties.

INTRODUCTION

The relationship between cancer and tropical diseases has been well established for years.

This paper will identify some obstacles to closer and broader ties between both research, show some common therapeutic drugs and mutual contributions and make general recommendations on how to improve the quantity and quality of work in both specialties.

DISCUSSION

The relationships between cancer and the inter-tropical zone are multiple. Indeed:

SOME CANCERS

- Are specific to or more prominent in tropical areas such as Burkitt's lymphoma or Kaposi's sarcoma.
- Have etiological factors found more frequently in tropical areas such as aflatoxins produced by molds in peanuts, which under different culinary preparations constitute an important part of the daily diet of many Africans. Aflatoxins are involved in the genesis of primary liver cancer, which is highly prevalent in tropical countries.
- Have a positive progression in many tropical countries whereas the opposite trend can be observed in some developed countries as for cancer due to smoking. This divergent evolution is largely due to (a) Aggressive marketing strategies of cigarette companies in third world countries and (b) Very restrictive government regulations in first world countries.
- Emerge in the course of AIDS (a disease which originated in the tropics), such as Kaposi's sarcoma, cerebral lymphoma and non-Hodgkin lymphoma.

SOME TROPICAL DISEASES

- Can lead to cancer such as bladder cancer in urinary schistosomiasis.
- Have cancer-like local evolution such as echinococosis or metastatic progression such as hydatidosis, when the cyst is ruptured.
- Can be found in patients immuno-depressed by cancer or its therapy such as candidiasis, disseminated aspergillosis, cryptococcosis, pneumocystosis, cryptosporidiosis, microsporidiosis, malignant strongyloidiasis, etc…

However, to this date the complementarity and overlapping of cancer and tropical disease research have been largely underestimated. Although they are both conducted first and foremost in developed countries, the reasons for this fact may be multiple, for example:

DIFFERENT TARGET POPULATIONS

While cancer patients reside primarily in first world countries, tropical disease patients overwhelmingly live in third world countries. These populations are further divided geographically: mainly in the Northern Hemisphere for

cancer and in the Southern Hemisphere for tropical diseases. Other gaps separate them such as (a) Age: globally older for cancer and younger for tropical diseases and (b) Wealth: rich in the North and poor in the South.

ISOLATION OF INSTITUTIONS

TROPICAL DISEASES DEPARTMENTS

For the longest time tropical diseases departments have been considered an oddity in the scientific and medical community and even relegated to a second-class category. Fortunately, this attitude has gradually been changing since 1983, year of the international emergence of AIDS.

CANCER CENTERS

In Europe and the United States cancer centers are highly sophisticated and sometimes isolated from other medical centers.

MUTUAL IGNORANCE

Cancer researchers generally don't know the implication of their works on tropical diseases. Nevertheless, anti-neoplastic compounds had and still have important roles to play in the treatment of tropical diseases.

Tropical diseases researchers have had limited access to cancer research centers and/or did not get the attention they deserved from authorities in this specialty. Moreover, despite the extent of the challenges they present, such as:

- Billions of people affected
- Global expansion for many of them (malaria, trypanosomiasis, dengue fever, etc)
- Parasite and vector drug resistance
- Minimal research for some neglected ones
- Forbidding therapeutic cost in unprosperous areas, etc,

tropical diseases are still not admitted as an independent field of medicine. They continue to be included into the infectious diseases curriculum in the United States and even in some tropical countries! This greatly diminishes their identification ability and undoubtedly hampers their attractive power to young researchers and practitioners.

Despite these limitations the synergy between cancer and tropical diseases therapeutic research has been significant, for example:

METRONIDAZOLE

Although well tolerated and efficient in humans and widely used in amebiasis, giardiasis, trichomoniasis and anaerobe infections, it has been shown to significantly increase the incidences of lung tumors in mice of each sex, lymphomas in female mice[1,2] and mammary, pituitary, testicular and liver tumors in rats[1,3,4]. It also increases the incidence of colonic tumors induced in rats by subcutaneous administration of 1,2-dimethylhydrazine[5,6].

FLUCYTOSIN

It is an important drug for treating systemic mycoses such as candidiasis, cryptococcosis, chromomycosis and aspergillosis. After administration, it is metabolized intracellularly into 5-fluorouracil by a specific deaminate cytosine enzyme[7]. Fluorouracil itself can be used against digestive tract adenocarcinomas, colorectal cancer, breast and ovarian cancer and squamous cell carcinomas of the upper respiratory and digestive tracts[7].

LEVAMISOLE

It is very efficient and well tolerated, even after the first trimester of pregnancy and was used in ascariasis[8]. It is also partially active in ancylostomiasis. In mice, its antitumor effects are mediated by NC-1.1+ cells[9]. The FDA has approved it in combination with 5-fluorouracil in the treatment of Duke's stage C colon cancer[10].

OLTIPRAZ

It is well tolerated and very efficient against Schistosoma haematobium, Schistosoma mansoni and Schistosoma intercalatum[11]. It has cancer anti oxidant protective actions associated with the induction of two enzymes mediated by a 41bp enhancer. It induces superoxide formation[12].

PROTEASE INHIBITORS

Widely used in HIV/AIDS, these compounds have other therapeutic properties:

- In cancer: Nelfinavir induces endoplasmic reticulum stress, autophagy and apoptosis in vitro and in vivo (in mice). Nelfinavir, Ritonavir and Saquinavir inhibit the proliferation of NSCLC cells as well as every cell line in the NC160 cell line panel. Nelfinavir is the most potent. It also decreases the viability of drug resistant breast cancer cells lines[13].
- In Chagas disease[14]:A cysteine protease inhibitor

has been shown to protect dogs from cardiac damage during infection by Trypanosoma cruzi[15]. Furthermore, it can cure T. cruzi experimental infections in mice[16].

INTERFERON ALFA-2BETA

It is a drug of choice in the treatment of chronic hepatitis C and B (the latter being the most endemic in Africa and Southeast Asia). It is also indicated in hairy cell leukemia, follicular lymphomas, and malignant melanoma in the USA[$_{17}$] and chronic myeloid leukemia, multiple myeloma and carcinoid tumors in France[$_{7}$]

RECOMMENDATIONS

In the interest of both disciplines, the magnitude and scope of their co-operation should be significantly enhanced at all levels. This thrust should take place nationally in various countries with the capacity to make significant progress in the treatment of cancer and tropical diseases such as, for example, the USA, France, Great Britain, Switzerland and Germany. This could occur between research centers, medical settings and pharmaceutical companies. The exchanges should also dramatically grow internationally between the same structures.

Unfortunately, leadership for this initiative will hardly come by given the current circumstances of extreme competitiveness and primarily mercantile interests best exemplified by the infamous Gallo-Montagnier dispute. The goal of this brief article is to serve as a reminder of the possibilities and potential rewards. Hopefully, it could be the first step in the right direction.

CONCLUSION

The collaboration between cancer and tropical disease researchers has long been marginal although they reciprocally benefited from their works. In order to meet successfully the very serious challenges of the 21st Century such as for example, emerging diseases, drug resistance, research and therapeutic cost, the author calls for deeper and wider ties nationally and internationally between scientists and practitioners of the two specialties, particularly in the therapeutic domain.

References

1. IARC monograms, 1977, (13):113-122
2. Cavaliere A., Bacci M., Amorosi A., Delgaudio M. and Vitali R. Induction of lung tumors and lymphomas in BALB/c mice by metronidazole. Tumori, 1983, (69):379-382
3. Rustia M. and Shubik P. Experimental induction of hepatomas, mammary tumors and other tumors with metronidazole in noninbred Sas:MRC(WI)Br rats. J. Natl. Cancer Inst., 1979, (63):863-868
4. Cavaliere A, Bacci M. and Vitali R. Induction of mammary tumors with metronidazole in female Sprague-Dawley rats. Tumori, 1984, (70): 307-311
5. Sloan D. A., Fleiszer D. M., Richards B. K., Murray D. and Brown R. A. Increased incidence of experimental colon cancer associated with long term metronidazole therapy. Am. J. Surg., 1983, (145):66-70
6. A-Kareem A. M., Fleiszer D. M., Richards G. K., Senterman M. K. and Brown R. A. Effects of long term metronidazole (MTZ) therapy on experimental colon cancer in rats. J. Surg. Res. 1984, (36):547-552
7. Vidal dictionary, "Editions du Vidal" publisher, 2001, p. 104
8. Moens M., Dom J, Burke W. E., Schlossberg S. and Schuermans V. Levamisole in ascariasis. Am J. Trop. Med. Hyg., 1978, (27):897-904
9. Clarke G. R., Burton R. C. and Smarty Y. C. The antitumor effects of levamisole in mice are mediated by NC-1.1+ cells. Cancer Immunol. Immunother. 1997, 45, (2):115-118
10. Cancerconsultants.com Oncology Resource Center. Class: Biologic agent. Generic name: Levamisole. Trade name: Ergamisol.
11. Gentilini M., Duflo B., Richard-Lenoble D., Brucker G., Danis M., Niel G., and Meunier Y. Assessment of 35972 R. P. (Oltipraz), a new antischistosomial drug against Schistosoma haematobium, Schistosoma mansoni and Schistosoma intercalatum. Acta Tropica, 1980, (37):271-274
12. Velayutham M., Villamena F. A., Fishbein J. C. and Zweier J. L. Cancer chemopreventive Oltipraz generates superoxide anion radical. Arch Biochem Biophys., 2005, 435(1):83-8
13. Gills J. J., Lopiccolo J., Tsurutani J., Shoemaker R. H., Best C. J. M., Abu-Asab M. S., Borojerdi J., Warfel N. A., Gardner E. R., Danish M., Hollander C. M., Kawabata S., Tsokos M., Figg W. D., Steeg P. S. and Dennis P. A. Nelfinavir, a lead HIV protease inhibitor, is a broad-spectrum anticancer agent that induces endoplasmic reticulum stress, autophagy and apoptosis in vitro and in vivo. Clinical Cancer Research, 2007, (13):5183-5194
14. Meunier Y. Chagas disease. In "Medecine Tropicale" by Gentilini M. and Duflo B. Flammarion publisher, 1986, fourth edition
15. Barr S. C., Warner K. L., Kornreic B. G., Piscitelli J., Wolfe A., Benet L. and McKerrow J. H. A cysteine protease inhibitor protects dogs from cardiac damage during infection by Trypanosoma cruzi. Antimicrob. Agents Chemother., 2005, 49, (12):5160-5161
16. Engel J. C., Doyle P. S., Hsieh I., and McKerrow J. H. Cysteine protease inhibitors cure an experimental Trypanosoma cruzi infection. J. Exp. Med., 1998, 188, (4):725-734
17. Physicians' Desk Reference. Medical Economics Thomson Healthcare publishers. 201 (55), p. 2903

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