IVERMECTIN should be given to all advanced Breast Cancer patients - outperforms chemo Paclitaxel and kills Cancer ...

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IVERMECTIN should be given to all advanced Breast Cancer patients - outperforms chemo Paclitaxel and kills Cancer Stem Cells!

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Another bombshell paper from Mexican researchers!

2017 - Dominguez-Gomez et al - Ivermectin as an inhibitor of cancer stem-like cells

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The aim of the present study was to demonstrate that Ivermectin preferentially inhibited cancer stem-like cells (CSC) in breast cancer cells and downregulated the expression of 'stemness' genes.

IVERMECTIN AND CANCER

Ivermectin, a polycyclic lactone pesticide produced by bacterium *Streptomyces avermitilis* is a broad-spectrum antiparasitic drug that has been used in human medicine since 1987

A study from 1996 (Didier et al) reported that ivermectin treatment in murine multidrug-resistant (MDR)-P388 and human MDR-CEM **leukemia cells** was a substrate and inhibitor of P-glycoprotein-mediated multidrug resistance in cancer

Another 2004 study (**Driniaev et al**) demonstrated that iIvermectin, at doses of 3–5 mg/kg, was able to **suppress the growth of human melanoma** and a number of other cancer xenografts in mice without adverse effects

In 2009 (**Gupta et al**), a high-throughput screen was performed to i**dentify the selective inhibitors of cancer stem-like cells (CSCs) and demonstrated that salinomycin treatment reduced the proportion of CSCs by >100-fold relative to paclitaxel,** inhibited mammary tumor growth *in vivo* and increased epithelial differentiation of tumor cells.

- Salinomycin is an antiparasitic drug for veterinary use only.
- In a search of 1623 compounds in DrugBank: **IVERMECTIN had highest molecular similarity to salinomycin.**
- it was hypothesized that IVERMECTIN may also possess similar biological properties

RESULTS:

Growth inhibition of the breast cancer cell line MDA-MB-231 by Ivermectin was investigated

Ivermectin demonstrated an inhibitory effect upon the growth of MDA-MB-231 cells in the range of 0.2-8 μM.

Ivermectin showed moderate dose-dependent antitumoral effects on MDA-MB-231 cells.

CANCER STEM CELLS

"Ivermectin preferentially inhibits the viability of CSC-enriched populations (CD44+/CD24- and cells growing in spheroids) compared with the total cell population. The opposite pattern was observed with paclitaxel treatment."

- **$CD44^+/CD24^-$ subpopulation of MDA-MB-231 cells has been previously reported to possess stem/progenitor cell properties,** and this subpopulation in patients with breast cancer exclusively **retains the ability to form novel tumors**
- The proportion of $CD44^+/CD24^-$ cells in the cell line MDA-MB-231 is 85±5%
- In addition, spheroids of cell lines growing in nonadherent conditions are also reported to be enriched in stem cells
- Therefore, these two conditions were used to determine **whether ivermectin treatment preferentially inhibited the CSC population compared with treatments with the cytotoxic drug paclitaxel.**

"Ivermectin preferentially inhibited the CSC subpopulation in the MDA-MB-231 cells and downregulated the expression of genes involved in the maintenance of pluripotency and self-renewal."

Ivermectin significantly reduced the expression of these three genes at both the mRNA and the protein level

The results of the present study demonstrated that Ivermectin, an antiparasitic drug for approved for human use, preferentially targeted the CSC-enriched subpopulation of the breast cancer cell line MDA-MB-231.

Higher reductions in cell viability were observed for the $CD44^{+}/CD24^{-}$ subpopulation and spheroids treated with ivermectin compared with paclitaxel.

These results were accompanied by the decreased expression of stemness genes nanog, sox-2 and oct-4, previously reported to be highly expressed in CSCs

Failure to successfully eradicate tumors no longer amenable to local treatments is at least partly due to the existence of CSCs, which are characterized by tumorigenic properties, such as self-renewal, formation of differentiated progeny and development of resistance to therapy.

CONCLUSION: "**In conclusion, results from the present study demonstrated that ivermectin preferentially targeted the stem cell population in MDA-MB-231 human breast cancer cells. Ivermectin has been demonstrated to be safe, following treatment of millions of patients with onchocerciasis and other parasitic diseases, which makes it a strong candidate for further studies investigating its potential use as a repurposed drug for cancer therapy.**"

My Take...

2023 Landeros et al - Cancer Stem-like Cells in Breast Cancer

Although the largest cell burden of a tumor is formed by the so-called bulk tumor cells, a small subpopulation of cells within the tumor has recently been identified, which presents a stem cell phenotype, due to the similarities to these cells have been called "cancer stem-like cells" (CSCs) or "tumor-initiating cells" (TICs) (**Figure 2**).

This cell population generally has the characteristic of unlimited self-renew, a hallmark of stem cells.

Thus, these cells can divide symmetrically, producing two daughter cells with stem cell properties, or divide asymmetrically, producing a daughter cell with stem cell properties and a second cell that integrates with the tumor mass through differentiation mechanisms [**24**,**25**].

The symmetrical division allows excessively increased tumor growth in response to stress conditions, such as cell loss during treatments [**26**].

The CSCs present high tumorigenicity, several studies have proposed that they participate in all stages of cancer development, and would be responsible for the initiation, maintenance, and progression of tumors.

In addition, they would participate in the expansion of the tumor to distant organs during metastasis and recurrence [**27**].

Cells 12 00720 g002

The lethal behavior of CSCs is mainly due to their tumorigenic capacity just described, but **these cells have also been shown to be more resistant to chemotherapy, endocrine therapy, and radiotherapy compared to bulk tumor cells** [**28**,**29**,**30**].

Accumulated evidence shows that **there is an increase in the CSC ratio after conventional treatmen**t [**31**]. Different mechanisms are involved in resistance to therapies, including the overexpression of

membrane transporter genes of the ATP-binding cassette (ABC) family, which encode proteins responsible for pumping drugs out of the cell. These cells are more resistant to chemotherapeutic agents; have increased DNA repair; increased aldehyde dehydrogenase (ALDH) activity, and can reduce intracellular reactive oxygen species levels [**32**].

Induction of epithelial–mesenchymal transition (EMT) has been shown to result in the acquisition of stem cell-like properties. EMT is characterized by decreased epithelial markers such as E-cadherin and upregulation of mesenchymal proteins (Vimentin, N-cadherin, and Fibronectin). These molecular alterations cause loss of apical polarity, **loss of cell-cell epithelial junctions, and promote a reorganization of the cytoskeleton which allows cancer cells to migrate, invade, and metastasize** [**33**].

My Take...

What are the implications of this incredible Ivermectin study from Mexico?

Ivermectin kills Cancer Stems Cells at more than 100-fold rates compared to leading chemotherapy (Paclitaxel or Taxol).

Ivermectin also downregulates expression of "stemness genes" which are highly expressed in Cancer Stem Cells. This is wild.

CANCER STEM CELLS **participate in all stages of cancer development, are responsible for initiation, maintenance and progression of tumors, participate in expansion of tumor to distant organs during metastasis and recurrence.**

So the obvious question is: why wouldn't you give Ivermectin to every Advanced Breast Cancer patient, to eliminate Cancer Stem Cells?

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