

Integrin Inhibitor Drugs: New Therapy Against Metastasis

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Abstract

The spread of cancer around the body-metastasis is one of the biggest challenges in cancer treatment. It is often not the primary tumor that kills, but the secondary growths. Cancer cells are able to break away from the primary site, travel around the body and seed new tumors. A key question in cancer research was how cancer cells are able to survive when they break away from a tumor to spread around the body. Cells are more protected when they are attached to other cancer cells and their surroundings. But they become more vulnerable if they detach and float and also normally undergo cell death. Metastasis is now seen as incurable and remains one of the key targets of cancer research. The question is how two molecules communicate and work together to help cancer cells survive during metastasis. We are presenting now in this article below one special drug case able to block the spread of cancer metastasis within the human body.

Keywords: Integrin; Metastasis; Naphazoline nitrate; Sanorin; Cancer treatment

Introduction

Human bodies have a network of lymph vessels and lymph nodes, as a part of the immune system. It collects fluid, waste materials, viruses and bacteria from the body tissues, outside of bloodstream. Lymph vessels carry the clear watery fluid called lymph. Lymph fluid would build up and cause swelling if it were not drained in some way. This is the role of the lymph vessels: draw up the lymph fluid from around the cells to send it towards the chest. There, lymph fluid collects into large vessel that drains into a blood vessel near the heart. There are hundreds of lymph nodes throughout the body and work as filters for harmful substances. They contain immune cells and are attacking, destroying germs carried in through the lymph fluid [1].

When there is a problem, such as cancer, the node or the group of lymph nodes in a given area may swell or enlarge as they work filter out the "bad" cells (lymphadenopathy). Swollen lymph nodes are signaling that something is not right. When more than one area of lymph nodes is swollen, it's called generalized lymphadenopathy. Cancers like lymphoma and leukemia can cause this kind of swelling [2].

If cancer cells break away from a tumor, they can travel to other areas of the organism through either the bloodstream or the lymph system to reach distant organs. When they travel through the lymph system, the cancer cells may end up in lymph nodes. Also one or two cancer cells might settle in a new area, begin to grow, and form new tumors. This spread of the cancer to a new part of the body is called metastasis [3].

In order for cancer cells to spread to new parts of the body, they have to go through several changes. They first have to be able to break away from the primary tumor and then attach to the outside wall of lymph vessel or blood vessel. Then they must move through the vessel wall to flow with the blood or lymph to a new organ or lymph node. When cancer grows inside lymph nodes, it affects the lymph nodes

near the tumor itself. These are the nodes that have been doing most of the work to filter out or kill the cancer cells [4].

Nodes that have been removed during cancer surgery can leave part of the body without a way to drain off the lymph fluid in the affected area. Many of the lymph vessels then run into dead end, and fluid can back up. This is called lymphedema and it can become a life-long problem. The more lymph nodes are removed, the more likely it is to occur back [5].

Research Letter

Cancer becomes metastatic when cells break away from the primary tumor and spread to other parts of the body. Metastatic cancer is much more difficult to treat and patients with metastatic cancer have a generally worse prognosis. The cancers that kill are those that spread to other parts of the body or disseminate within the organ. If we could keep cancer cells confined to the primary tumor mass, it is possible to remove it with less risk of metastasis and later recurrence [2].

A novel mechanism of more selective ways to stop cancer cells from spreading. Researchers have identified the role of the protein RSK2 in cancer cell migration, part of the process of cancer metastasis. RSK2 significantly increases cell migration by influencing integrin activations. Integrin play an important role in cell adhesion to their surrounding tissue and the migration of tumor cells to new location in the body. RSK2 is active in both breast and prostate tumors, and promotes proliferation in these cells. It can also promote cell invasion and metastasis in the head and neck tumors in addition to lung cancer and neuroblastoma.

Recently many research teams are focusing on understanding the process of cell adhesion. Integrins help the cell move by grabbing onto proteins and cell surroundings, pulling, then releasing and grabbing on again. Blocking a cancer cell's ability to adhere and move can control further dissemination of some metastasis.

There are drugs that kill cancer cells and there also drugs that stop the division of cancer cells, but there are far fewer drugs that specifically stop the movement of cancer cells. We hypothesize that

drugs that interfere with RSK2 may help control or prevent metastasis. New research can lead to selective ways to inhibit metastasis of a subset of tumors.

Case Study: Patient 1

After complete internal control were diagnosed in October 2009, with colorectal cancer at the healthcare center Bratislava, Mýtna ul., Slovakia. Patient is male, age at the time of diagnosis 59 years (now 66 years), his first problems were the enlarged, swelling lymph nodes at the region of the neck. Identifying the presence or absence of metastatic cancer in a patient's lymph nodes was the critically important task of diagnose for pathologists.

The general rate of metastasis- (the chemotherapeutic treatment was not introduced): Treatment of cancer is based on the type of cancer a person has, and the stage of the cancer. We are using a system to assign a stage to the cancer. The most common staging system is the TNM system. The T in TNM stands for tumor, the M stands for metastasis, and the N stands for lymph nodes. If there is no cancer found in the lymph nodes near the cancer, the N is assigned a value of 0. If nearby or distant nodes show cancer, the N is assigned a number such as 1, 2 or sometimes 3, depending on how many nodes are affected, how much cancer is in them, how large they are, and where they are. Generally, is accepted that cancer with lower TNM numbers is usually easier to treat and has a better outlook for survival. In our patient case it was: T2, N3, M2, it means that the cancer was spread.

During these last 7 years until up to date he has been not absolved no one treatment procedure of the surgery, radiation or chemotherapy [3].

Case Report

Here we report the case of a 66-year-old man suffering from colorectal cancer, whose treatment is possibly related to the naphazoline nitrate nasal decongestant.

Conclusion: The use of naphazoline nitrate may result in an analgesic effect upon first use, through activation of adrenergic and opioidergic systems, followed by a pro-migraine effect via a late induction of an inflammatory cascade, modulated by nitric oxide and arachidonic acid.

Cancer cells appear to depend on an unusual survival mechanism to spread around the body. The discovery of the above mechanism could help also to us in analysis of our case study and our novel treatment to prevent metastasis and secondary tumors during as minimum last seven years.

To analyze our discovery of drug usable against metastasis we are outgoing from the study from nature communications [6]. The researchers revealed a previously unknown survival mechanism in cancer cells, in which the molecules known as 'integrins' could be the key.

Naphazoline (in the hydrochloride form) is the common name for 2-(1-naphthylmethyl)-2-imidazoline hydrochloride (Figure 1). It is a sympathomimetic agent with marked alpha adrenergic activity. It is a vasoconstrictor with a rapid action in reducing swelling when applied to mucous membrane. It acts on alpha-receptors in the arterioles of the conjunctiva to produce constriction, resulting in decreased congestion. It is an active ingredient in several over-the-counter formulations including Clear Eyes and Naphcon eye drops. It has the molecular

formula $C_{14}H_{14}N_2$ and a molar mass of 246.73 g/mol. A possible association with stroke has been suggested [7].

Naphazoline

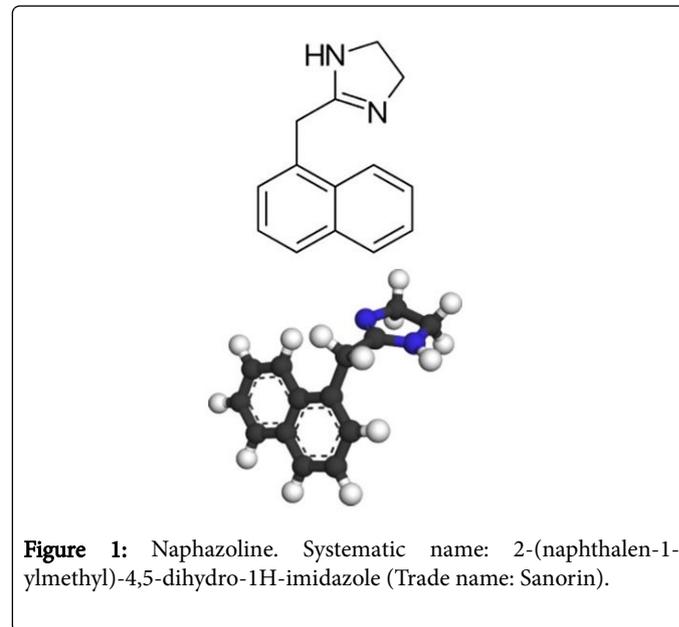


Figure 1: Naphazoline. Systematic name: 2-(naphthalen-1-ylmethyl)-4,5-dihydro-1H-imidazole (Trade name: Sanorin).

Naphazoline Nitrate: Sanorin 1%

Decongestant drops/spray-Nasal, is used to decrease the swelling of the mucus membrane. It is produced by Teva Czech Industries S.R.O., 747 70 Opava, Komárov, Czechia. When lymph fluid was build up and caused swelling, then naphazoline nitrate could drain it in to some way decrease the swelling. It is basically administered against runny nose, the snuffles. naphazoline nitrate as new integrin inhibitor drug target the adhesive function of cancer cells and block them on their surface. Success of our case study drugs therapy could be explained by this newly discovered role of integrins within the cancer cells.

This medication is used for temporary relief of congestion in the nose caused by various conditions including the common cold, sinusitis, hay fever, and allergies. It works by narrowing the blood vessels in the nose area, reducing swelling and congestion. This drug may also be used to relieve "plugged ears" and to reduce swelling in the nose before certain surgery or procedures.

Seek medical attention right away if any of these severe side effects occur while taking naphazoline nasal: Severe allergic reactions (rash; hives; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); changes in vision; eye pain; worsening or persistent eye irritation or redness. It is possible that some side effects of naphazoline nasal may not have been reported [8,9].

Conclusions

Integrins are proteins on the cell surface that attach to and interact with the cell's surroundings. 'Outside-in' and 'inside-out' signaling by integrins is known to help the cancer cells attach themselves to their surroundings. When the cancer cells are floating, as they do during metastasis, the integrins switch from their adhesion role to take on a new form of communication which was unknown 'inside-in' signaling, in which integrins signal within the cell.

An integrin called beta-1 ($\beta 1$) pairs up with another protein called c-Met and they move inside of the cell which is normally used to degrade and recycle cell material. Instead the location is used for a new role of cell communication and the two proteins send a message to the rest of the cell to resist against death while floating during metastasis. Metastases were less likely to form when ($\beta 1$) and c-Met were blocked from entering the cell together or were prevented from moving to the special location within the cell [6].

Integrins are already major targets for cancer treatment with drugs either being tested or in use in the clinic. As integrin inhibitor drug target their adhesive function and block them on the surface of the cancer cell. Success of our case study drugs therapy could be explained by this newly discovered role of integrin's within the cancer cells.

We have many years long successful experience with our new strategy of cancer treatment given by prevention of the integrin from going inside the cell in the first place. We have now a better therapy against metastasis in the whole known World! Our therapy represents a more effective treatment of metastasis with naphazoline nitrate that is blocking cancer by slowing to zero both tumor growth and spread [3].

As our definitive conclusion we must underline that during these last 7 years until up to date our patient 1 has been not absolved no one treatment procedure of the surgery, radiation or chemotherapy.

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