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LETTER TO THE EDITOR

An oncolytic parasite to treat polycythemia vera

In recent years, there has been a surge of clinical trials to treat various kinds of cancers with non-replicating versions of viruses (1). The most famous among these is the recent use of a genetically engineered poliovirus used to treat one of the most difficult-to-treat and recurring cancers – Glioblastoma Multiforme (2, 3). In addition, various other modified viruses are being exploited to treat melanoma, lymphoma, and other tumors. To the best of our knowledge, there has been no report on the potential use of oncolytic parasites in the treatment of cancer. Here, we propose the use of a non-pathogenic strain of *Plasmodium knowlesi* to treat primary polycythemia vera (PV) or other myeloproliferative diseases (4). *P. knowlesi* was widely used to treat syphilis before the advent of penicillin (5, 6).

A PV is a chronic myeloproliferative disorder of the total bone marrow without any evidence of invasiveness, in which erythrocytosis, leukocytosis, and thrombocytosis are simultaneously present (4, 7, 8). PV is a hematopoietic stem cell disorder characterized by a pan hyperplastic and neoplastic bone marrow and is classified as a myeloproliferative disease. Polycythemia vera, also known as polycythemia rubra vera (PRV), is characterized by an elevated absolute red blood cell (RBC) mass because of unrestrained RBC production. The gold standard for therapy is systematic phlebotomy (8). In refractory cases, radioactive phosphorus is used (8). However, the radioactive therapy carries its own side effects (8).

Similar to oncolytic viruses that enter a specific histological tumor cell type(s) that expresses a well-defined entry receptor(s) for the virus, *P. knowlesi* also targets RBC (9, 10). This oncolytic parasitic treatment for PRV may be looked upon as an innovative treatment of the 21st century since most contemporary physicians may be unaware of it.

The *Plasmodium*-based treatment can be administered by intravenous injection of the cultured *P. knowlesi* as needed and it is non-pathogenic to humans. The parasite causes a high fever infecting RBC and, after few 24-h cycles of replication, self-terminates without any treatment. This parasite was used routinely from 1937 to mid-1950s to cure syphilis. In the pre-antibiotic era, the goal of 'malariotherapy' was to cause high fever that killed *Treponema pallidum*. This procedure can be repeated every few months, eliminating the need for phlebotomy. The treatment has high potential, in particular, in developing nations and remote rural areas of the globe where phlebotomy, using non-sterile needles, is commonplace. Clearly, during the latter, post-phlebotomy infection can become problematic. Lyophilized *Plasmodium* parasites can survive for years in a dry and non-refrigerated environment, and may be quickly hydrated by sterile water prior to their injection. The high fever, generally associated with parasitemia, can be dampened by anti-pyretics, since the purpose of this innovative proposed therapy is not to cause high fever but to lyse RBC and reduce RBC overload to near normal. It is probable that this treatment may temporarily cause anemia in some individuals. Since the underlying pathology being a myeloproliferative disorder resulting in excess RBC production, anemia may not be severe or it may not even occur (1–3, 11). The treatment may also be associated with hepatosplenomegaly. This may occur as a result of increased activity of reticuloendothelial system in an attempt to phagocytize infected RBCs. Another potential adverse effect with 'malariotherapy' may be hemoglobinurea secondary to hemolysis resulting from lysed parasitized RBCs. Hemoglobinurea can culminate in acute tubular necrosis causing renal damage. In case of the latter, cautious fluid intake is usually sufficient to reverse any renal impairment.

Historic use of *P. knowlesi*

Plasmodiums of various species have been in use to treat syphilis since 1917. In 1917, Julius Wagner von Jauregg was the first to use a benign *Plasmodium vivax* to treat syphilis (11). This was originally inspired by the discovery of Schaudinn (5) that the causative agent of human syphilis, *T. pallidum*, was temperature sensitive and the spirochetes could be killed at several degrees above the normal human body temperature of 98.6°F (5, 11). Thus, an elevated temperature that was tolerable to humans but killed *T. pallidum* was identified (5, 11). von Jauregg hypothesized that if humans suffering from syphilis were infected with malaria, the increase in body temperature to 104°F would cure this disease. To test his hypothesis, von Jauregg began treating syphilitic patients in efforts to induce high fever every 48-h (11). This stroke of brilliance was right on the mark, since this parasite is an excellent pyrogenic agent that can be controlled easily by treating the parasite with anti-malarial agents, such as quinine, that were readily available at that time. This 'malariotherapy' won a Nobel Prize in 1927 for its discoverer, was effective, but there were logistic issues! The major one was the lack of a regular supply of the parasite. In 1917, neither freezers nor lyophilization techniques were available, nor were available any appropriate animal models or

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cell culture methods that would have enabled maintenance of a constant supply of the parasites. One needed a better source of *P. vivax* other than the human 'volunteers' that were employed as hosts (5, 11). This was really challenging because it was difficult to keep the 'volunteers' in a state of fever on a regular basis, since unless they had parasitemia, live parasites could not be isolated from their blood. An unexpected discovery solved this problem. In 1932, when India was still a British colony, scientists in Calcutta School of Tropical Medicine discovered that the Malayan irus monkey was a natural host to a species of *Plasmodium* (later named *P. knowlesi,* after its discoverer Robert Knowles) that caused no apparent illness. However, if inoculated to Indian rhesus monkeys or humans, the parasites can cause mild malaria and were pyogenic. In humans, this new parasite replicates in blood, with regular 24-h high-fever cycles, and self-terminates without treatment. This new erythrocytic parasite became an ideal pyogenic treatment for syphilis. In the 1920s and 1950s, there were many clinics worldwide that practiced 'malariotherapy' for syphilis, and in 1937 a well-known clinic in Bucharest, Romania, initiated the first large-scale malariotherapy for syphilis with *P. knowlesi* and continued the therapy until the 1950s when penicillin became a routine mode of therapy for syphilis and other infections (5, 11). In addition, many other clinics used 'malariotherapy' on a large scale to treat syphilis. For example, in England's Horton Hospital alone, there were over 10,000 patients who were treated with *Plasmodium* between the 1920s and 1950s (5, 11).

Our present hypothesis, to treat the refractory cases of PV, was prompted by the current surge of virotherapy for various kinds of neoplasia. There is a surge of research and clinical trials using genetically engineered oncolytic viruses to treat different kinds of cancers (1–3, 12). We believe that it will not be long before new genetically engineered oncolytic bacteria, bacteriophages, and other microorganisms will be available as oncolytic agents for various types of cancers. As opposed to oncolytic viruses where generally no antiviral agents may be available, antibiotics of various kinds can curtail oncolytic bacteria and parasites.

Accordingly, we propose that anti-cancer therapy should not be limited to oncolytic viruses but extended to other microorganisms as well as bacteriophages that can be readily utilized to treat many chronic neoplastic diseases, including PV. We forward the hypothesis that human PRV, a form of RBC neoplasia, can be treated with a non-pathogenic strain of *Plasmodium – P. knowlesi*, which can be described as an oncolytic parasite.

Authors' contribution

STR wrote part of the manuscript and OB conceived the idea and wrote the manuscript.

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