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Treatment of a High Grade Glioma (GBM) with four different oncolytic viruses (Parvo HI, VSV, NDV-Nothabene and Sindbis-Virus), elected by the symptoms, delivered via an Intra-arterial Port-a-Cath-System and controlled by repeated MRIs

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Treatment of a High Grade Glioma (GBM) with four different oncolytic viruses (Parvo HI, VSV, NDV-Nothabene and Sindbis-Virus), elected by the symptoms, delivered via an Intra-arterial Port-a-Cath-System and controlled by repeated MRIs

Summary

This is the first case report using different viruses to attack one tumour. They were chosen by the very unique method of human medicine: The patient, i.e. the highest authority, was asked to observe the development of the most conspicuous tumour associated symptoms in the course of therapy. The tumour was located in the gyrus cinguli on the right side of the frontal lobe, depressing the right ventricle and causing weakness of the left arm and leg. At the beginning of treatment the degree of these symptoms was estimated as 100%. Improvement was noted by a number below one and worsening by a number above 100%.

This simple method allowed the election of four different viruses that showed to be effective to influence the leading symptoms. In the beginning of the therapy the tumour growth was 100% within 5 weeks. At the first control 5 weeks later the growth slowed down to 50%. The second and third control showed "stable disease" and the following controls showed an increasing relief of pressure on the side ventricle accompanied by the reduction of the tumour-size.

History

The first observation that virus can lead to healing of even the advanced cancer was made by an Italian gynaecologist in 1904 called "peace": DePace.[1]

The 20th century gained a lot of experience, that naturally occurring viral diseases and deliberately applied viruses can influence the course of malignant diseases even to a point that we can call "cure"![2]

Quite often, however, the initial response was followed by a failure due to the well-known ways of escape: antibody production and selection of resistant clones. Both mechanisms have to be considered to help virotherapy on the way to success.

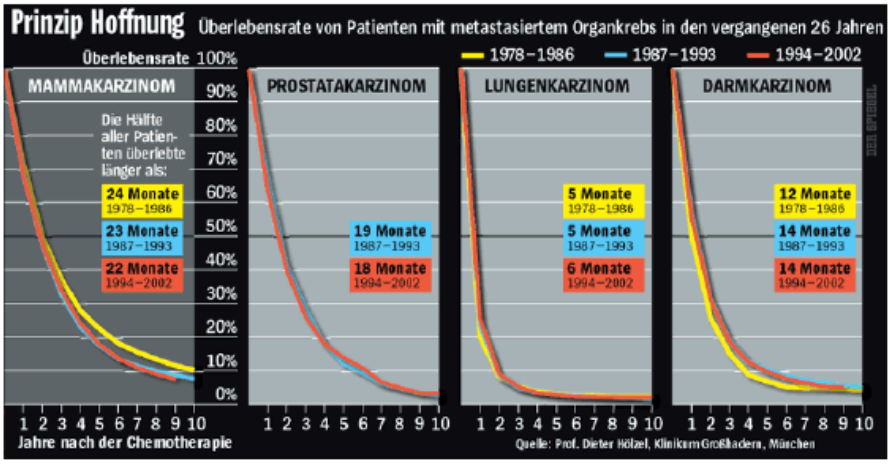
One simple strategy is to change the virus or the other is to combine several viruses in face of the fact that the tumour certainly consists of different clones with different degrees of "sensitivity" or rather "resistance".

At present there are 72 clinical trials being performed worldwide to evaluate different oncolytic viruses, mostly REO-Virus and a lot of genetically engineered Vaccinia-Viruses.

Chemotherapy was the great hope that suppressed all other approaches like fever and virotherapy.

At the end of this warring century we must confess: We have lost the "war against cancer". [3] There must be something wrong in our approach!

This is the Oath of Disclosure: „Poisoning without Benefit": It is the sober end result of a century's fight against cancer!



Spiegel 41/2004

Philosophy

It is very simple: Cancer behaves like a parasite, e.g. like a bacterium.
We have abundant knowledge about how to fight against parasites: to elaborate an "antibiogram".
The tradition of this knowledge forces us to elaborate a "virogram" in order to find out the most potent viruses for a given tumour!
The "virogram" is undoubtedly the solution of the problem, but it is not easily achieved.
We have to establish a cell line of the patient's own cancer.
The cancer cells that easily grow in tissue cultures, however, are not necessarily identical with the original tumour. It might be merely a laboratory adapted tumour strain without any significance in the clinical situation!
The solution of this problem is the comparison of the original tumour with the cultivated tumour cells with the help of molecular genetics in order to guarantee the identity. At least the hormonal status and the proliferative status must coincide!

Mostly we do not have tumour material of sufficient vitality at our disposal to establish a long term cell line and to perform an "in-vitro-virogram". This forces us to rely on the three clinical criteria of tumour response: symptoms, tumour markers and imaging, in order to elaborate an "in-vivo-virogram".

In the future we have to find out molecular patterns of the tumour cells that signalize "sensitivity" like in the case of K-ras-mutation and REO-virus type 3. For most types of tumours and viruses it is unfortunately yet unknown.

In our case we neither had living tumour material nor a tumour marker. This reduced our tools to "symptoms" and "imaging".

Method

Like in the case of the antibiosis of an unknown micro-organism we have to rely on the literature and on our own experience.

Parvo H1 is a virus which naturally occurs in rats. It does not even cause any symptoms in the natural host, not to mention the people. This virus is currently investigated by the German Research Institute in relapsing GMB.

VSV is the acronym of Vesicular Stomatitis Virus, causing a disease in cattle resembling foot-and-mouth-disease. Farmers are usually not afflicted. Sometimes they get a fever attack. It is clinically investigated in primary Hepatocelllular Carcinoma. An animal study showed high efficacy in GBM.[4]

Sindbis-Virus is endemic in Scandinavia and causes a disease in wild birds.
The Wollmanns animal study was also fairly effective in the case of GBM, even though to a lesser extent compared with VSV.

Newcastle-Disease-Virus (NDV) is the causative agent of atypical fowl-plague. It has been intensively investigated by Csatary since the sixties of last century in different tumours among others GBM6. They named their strain MTH-68/H, an acronym for "**M**ore **T**han **H**ope" in the year 1968 in Hungary. This strain is genetically nearly identical with the NDV-strain Mukteshvar.
Our strain is a mutant of MTH-68/H. It showed to be the most effective compared with four other strains in terms of oncolytic capacity and immune stimulating properties.7

The case report

10/10	First symptom: Grand Mal seizure MRI: Tumour in the right frontal lobe
05.10.10	Operation: Macroscopically complete resection (University of Regensburg) Histology: (UKR, H 23573/10): Glioblastoma WHO Grade IV, MGMT-Promotor methylated (100%), confirmed by the Reference Institute for Brain Tumours, Bonn, R-46851.

10-12/10	Radio-Chemo-Therapy until 60Gy, accompanied by Temozolomide 75mg/m2 daily together with radiation and Cilengitide 2g i.v. 2 times per week (Centric-Trial, Verum-arm). Cilengitide is a cyclic pentapeptide, that inhibits integrin, a trans-membrane protein essential for signal transduction, leading to an inhibition of angiogenesis.
1-7/11	Adjuvant Chemotherapy with Temozolomide 200mg/m2 d1-5/28 and Cilengitide 2g i.v. 2 times a week (six cycles)
7/11	MRI Relapse in the region of the right gyrus cinguli
15.07.11	Stereotactic radiation 6 x 5Gy
30.07.11	Intensified chemotherapy with Temozolomide 100 mg/m2 d1-7, 15-21/28 (4 cycles)
15.11.11	MRI: PD
19.11.11 1.	Cycle CCNU 110 mg/m2 d1/42, plus Procarbazin 60 mg/m2 d8-21/42, termination after the first cycle because of myelotoxicity (thrombocytopenia)
23.12.11	MRI PD: 26 x 20 x 30 mm = 16 ml, i.e. doubling of the tumour-volume within 5 weeks
23.12.11	Start of "specific detoxification"8
09.01.12	Start of virotherapy with Parvo-H1
30.01.12	MRI: PD: 27 x 26 x 31 mm = 22 ml, i.e. slowing down of the rapid volume increase from 100% to 50% within five weeks
07.02.12	Port implantation into the Aorta thoracica, ascending part (via the right subclavian artery)
02.04.12	MRI: Tumour volume 30 x 22 x 33 mm = 22 ml, i.e. stable disease since 8 weeks
08.06.12	MRI: SD since 12 weeks
25.07.12	MRI: Minimal regression
01.10.12	MRI: Further minimal regression. The ventricular system is "blooming up".

Fig. 2, 3, 4, 5

Summary

This case report is the proof of principle that clinical signs can be beneficial to choose an appropriate virus for an individual patient.
With the first virus (Parvo-H1) the increase of strength could be noticed after 3 – 4 days of daily administration.
With the second virus (VSV) the response was very dramatic: Within two hours the patient felt an increase of weakness in the left leg from 50% to 200%. It reached its climax after two more hours:

The patient fell down when trying to reach the toilet. Then the worsening slowly subsided within 12 hours, the final level of weakness was 40%.9
The response to the other viruses was not as conspicuous.
A second sharp rise of weakness was noted in connection with an inadvertent flu. The causative agent, however, remained in the darkness of clinical reality.
The hypothesis underlying this compassionate treatment, where all other modalities failed, is very simple:
The tumour behaves like a parasite. Oncolytic viruses share some common features with antibiotics.
These are the common features:
1. Resistance can occur, either primary or as a consequence of selection in the course of therapy.
2. A standardized "virogram" in analogy to the antibiogram could be of great help to choose the right virus for an individual tumour.10
3. In the case of "escape" we have to change the virus or to combine it with other viruses.

The main difference is the response of the immune system:
In the case of antibiosis it may lead to allergic reactions, due to the production of antibodies and cytotoxic lymphocytes.
In the case of virotherapy the immune response is ambivalent:
Antibodies antagonize the viruses, thereby diminishing their efficacy.11
The cytotoxic lymphocytes on the other hand work synergistically with the viruses: They do not directly attack the viruses but the virus-infected tumour cells.

"Modern times" are ruled by "trials", double blind if possible!
The status of "case reports" is steadily declining.
Biologists have taken over the fate of medical research.

This is a very doubtful evolution last but not least from a philosophical point of view:
The trial only throws light on the "collective" aspect of man.
It leaves the "individual" out of consideration.
The "individuality", however, is the essential difference between humans and animals, apart from "freedom" and "philosophy".

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   Wilder O. Oncolytic viruses as therapeutic agents.Ann. Med. 2001; 33(5): 291-304,
   Kelly E, Russell SJ, History of Oncolytic Viruses: Genesis to Genetic Engineering. MolTher 2007; 15(4): 651 – 9.
3. Nixon's ambitious program
4. Wollmann, G., Tattersall P., van denPol, A., Targeting Human Glioblastoma Cells: Comparison of Nine Viruses with OncolyticPotential, Journal of Virology, May 2005, p. 6005-6022
5. Csatary, L.K., Eckhardt, S., Bukosza, I., Czegledi, F., Fenyvesi, C., Gergely, P., Bodey, B., andCsatary, C.M.: AttenuatedVeterinary Virus Vaccineforthe Treatment ofCancer, in: CancerDetectionandPrevention, 17(6):619-627, 1993
6. Csatary, L.K.,Gosztonyi, G., Szeberenyi, J., Fabian, Z., Liska, V., Bodey, B., Csatary, C.M., MTH-68/H oncolytic viral treatment in human high-grade gliomas. Clinical Study, in: Journal of Neuro-Oncology 67 (2004), 83-93
7. Apostolidis, L., Schirrmacher, V., Fournier, P., Host mediated anti-tumoreffect of oncolytic Newcastle disease virus afterlocoregionalapplication, International Journal of Oncology 31: 1009-1019, 2007
8. The term „specific detoxification" refers to the application of homoeopathic preparations of those poisons that are likely impairing the immune systems, e.g. all past chemotherapies. As a consequence the side effects are promptly improved and quite often also tumour markers to a certain extent. This is a matter of fact even though the mode of action is completely unclear.
9. In Wollmanns animal experiment VSV was the fastest virus. Nevertheless the velocity of clinical response is difficult to explain.

However, medicine is an empirical science:

Facts do have priority

We cannot reasonably question the facts without declaring the patient an idiot. The lack of explanation cannot be the reason to deny somebody the soundness of mind. The lack of explanation is first of all my own deficiency! Facing the fact that 100.000 chemical reactions are taking place each second in a single cell, i.e.1018 in the whole organism (1 million times 1 million times 1 million!), it is not very surprising that unexpected events occur, on the contrary: It is very surprising, that any of our predictions really occur!

10. It is very amazing that this natural aim has not even been contemplated by the leading cancer research institutes. A generalpractitionerhasbroughtforththisidea:
    Thaller, A., Tumortherapie mit onkolytischen Viren unter Leitung der PCR zur Erstellung eines Virogramms und zur Therapiekontrolle, Wien 1999.
    In the absence of a standardized individual virogram we have to elaborate molecular patterns to predict "sensitivity" and "resistance".
11. They never cause allergic reactions against the virus itself but rather against contaminations by the culture medium, e.g. against egg proteins in the case of NDV cultured on egg cells and not on human tumour cells.