Potentially New And Innovative Treatments For Superficial, Muscle-Invasive, And Metastatic Transitional Cell Carcinoma (TCC) Of The Bladder

I Secasan, D Pop, C Secasan

Citation

Abstract
Purpose: To present a novel, innovative treatment for superficial, muscle-invasive and metastatic transitional cell carcinoma (TCC) of the bladder, which is based on a combination of:

1. A currently used anticancer drug (or a combination of anticancer drugs) - (DRUG-x)
2. A specific, autologous anti-cancer vaccine, VAX-x, made of in-vitro-heat/radiation-killed (IVHRK) cancer cells (or subunits of such cancer cells), prelevated from the patient, and bearing on their genomic/biochemical structure the mutations that would be induced into these cancer cells by the following, to come anticancer drug, or anticancer drugs combination (DRUG-x).

The subunits of the in-vitro-heat/radiation-killed (IVHRK) cancer cells may be certain proteins, enzymes (e.g. telomerase), DNA, or other cancer-cell antigens, bearing on their genomic/biochemical structure the mutations that would be induced into these cancer-cell parts/subunits by the following, subsequent, to come anticancer-drug, or anticancer-drugs combination (DRUG-x), and may form the VAX-x component of the (VAX-x, DRUG-x)-couple. We define the combination of a specific anticancer drug (DRUG-x) and its pre-(DRUG-x)-admininstered, corresponding, autologous cancer vaccine (VAX-x), made of in-vitro-heat/radiation-killed (IVHRK) cancer cells from the patient, and bearing on their genome the mutations that would be induced into these cancer cells by the specific drug (DRUG-x), as a (VAX-x, DRUG-x)-couple. The order of the 2 components within the (VAX-x, DRUG-x)-couple clearly indicates that the autologous, (therapeutic), anti-cancer vaccine, (VAX-x), is pre-administered to its corresponding (DRUG-x) couple-partner. The role of VAX-x, within a (VAX-x, DRUG-x)-couple, is to prevent the emergence of DRUG-x-resistant cancer cells (since it contains/encodes/encompases the drug-resistance-mutations that would be induced into cancer-cells by couple-partner DRUG-x), whereas the role of DRUG-x is to kill DRUG-x-sensitive cancer cells, in order to cure bladder cancer in particular, and any other type of cancer in general. The existence of (VAX-x, DRUG-x)-couples is made possible by the process of mutagenesis, and is based on the need and capacity of cancer cells (and living pathogens) to mutate under drug-pressure.

Materials and Methods: The Internet was used in order to locate and collect some of the most relevant scientific articles necessary to review the current status of bladder-cancer treatment, and we have used our own creativity and innovative imagination in order to develop a successful and powerful strategy and practical solution for curing bladder cancer in particular, and all other cancer types in general.

Results: The term (vaccine-drugs)-couples, (VAX-x, DRUG-x)-couples, has been invented, defined, and coined, and thus a new strategy and concept to cure bladder cancer has been developed. (VAX-x, DRUG-x)-couples may prove to be far more efficient and powerful in curing superficial, muscle-invasive, and especially advanced-metastatic bladder cancer. (VAX-x, DRUG-x)-couples may prove to be a far better option for treating superficial bladder cancer than BCG-immunotherapy plus chemotherapy, since VAX-x is defined as a specific, autologous vaccine, compared to BCG which is a non-specific vaccine, and since the synergy between VAX-x and DRUG-x is practically perfect, while synergy between BCG and chemotherapy is not always synchronized or sinergetic. Also (VAX-x, DRUG-x)-couples may prove to be a much better choice for treating...
muscle-invasive and metastatic bladder cancer than currently used standard chemotherapy (MVAC), since (VAX - x, DRUG - x)-
couples, at limit, may be written as (VAX - x, MVAC- x)- couples, and the sinergy between VAX - x, MVAC- x and the immune
system would represent an impressive plus in comparison with MVAC alone. The adverse local and systemic effects, side
effects, and toxicity of (VAX - x, DRUG - x)- couples may be significantly lower than those associated with BCG immunotherapy +
chemotherapy and also considerably lower than those seen with current standard chemotherapy (MVAC) for muscle-invasive
and metastatic bladder cancer. (VAX - x, DRUG - x)- couples and especially (VAX - x, MVAC - x)- couples may be able to cure
superficial, muscle-invasive and even metastatic bladder cancers.

Conclusions: (VAX - x, DRUG - x)- couples may prove to be able to cure superficial, muscle-invasive, and even metastatic
transitional cell carcinomas (TCC-s) of the bladder, and especially those (TCC-s) which are refractory to current standard
treatments and to all other existing alternative treatments. In addition, (VAX - x, DRUG - x)- couples may prove to be far more
efficient and effective in curing superficial, muscle-invasive, and metastatic bladder cancers, as well as all other types of
cancers, and to be less toxic than comparable current conventional therapies, having the potential to become the standard
treatment of care and cure for all bladder cancers, for all other types of cancer, and for absolutely all infectious diseases for
which at least one drug exists. Thus representing a revolution in modern medicine. The existence of (VAX - x, DRUG - x)-
couples is made possible by the process of mutagenesis, and is based on the need and capacity of cancer cells (and living
pathogens) to mutate under drug-pressure. The (Telomerase, MVAC - x)- couple might become one of the most powerful
anticancer therapies, by possibly being able to cure high-stage and metastatic bladder cancer, as well as all other types of
cancer.

INTRODUCTION

The successful treatment of bladder cancer remains a challenge for urologists and oncologists. There have been
substantial changes in the therapeutic options for the management of superficial, muscle-invasive, and metastatic
bladder cancer in the first 4 years of the new millennium.

For superficial bladder cancer, intravesical instillation of chemotherapeutic agents after transurethral resection is the
standard of care. Novel therapeutic approaches under investigation include anti-cancer vaccines ([1a]),
antisense oligodeoxynucleotides ([1b]), magnetically targeted carriers ([1c]) and bio-adhesive microspheres
([1d]).

For muscle-invasive bladder cancer, systemic perioperative chemotherapy is being used with increasing frequency and the
latest preclinical research efforts are focused on the inhibition of angiogenesis and other processes predisposing
to metastatic disease.

So far, treatment goals for bladder cancer of any stage have been complete removal of the initial tumor, prevention of
recurrence and progression to advanced disease with the ultimate aim of reducing mortality. The myriad of novel
therapeutic modalities currently being explored suggest that bladder cancer will soon become a long-term manageable
disease.

CURRENT TREATMENTS OF SUPERFICIAL
BLADDER CANCER (IE, CARCINOMA IN SITU,
TA, AND T1)

Superficial bladder cancer can be resected with minimal morbidity, but the patients remain at high risk for tumor
recurrence and progression. Tumors can be divided into low-, intermediate-, and high-risk categories based on tumor
grade, stage, and pattern of recurrence. Low-risk tumors are best treated with a single instillation of chemotherapy such
as thiopeta, doxorubicin, or mitomycin.

Intermediate-risk tumors can be treated with chemotherapy, but, similar to high-risk tumors, will often require
immunotherapy. High-risk tumors are best treated with intravesical bacille Calmette-Guerin (BCG) using a 3-week
maintenance schedule. Side effects of BCG immunotherapy can be reduced by logarithmic reductions in the dosage of
BCG. Patients who fail BCG may be rescued with BCG plus interferon-alpha or radical cystectomy.

Many patients with superficial bladder tumors treated with endoscopic surgery alone have recurrence or tumor
progression at some point in their follow-up, and, in these patients, the need for adjuvant treatment becomes a major
concern.

One of the most potent immunotherapies presently used is the application of Bacillus Calmette Guerin (BCG) to
prevent recurrences of superficial bladder cancer. Despite its successful use, nonresponders and certain side effects remain
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a major obstacle.

In 2002 Sylvester et al ([13]) carried out a meta-analysis of randomised trials that showed that intravesical BCG (following transurethral resection) reduced the risk of progression in papillary tumours and carcinoma in situ (CIS) when maintenance BCG was used. However, the adverse local and systemic effects, side effects, and toxicity of BCG should not be neglected, and in low risk patients intravesical chemotherapy is considered to be the optimal treatment.

Current studies aim at developing recombinant BCG (rBCG) strains to further improve the effectiveness of the therapy. In BCG-treated patients a strong local induction of Th1-like cytokines was observed. For this reason rBCG-strains secreting Th1-like cytokines might be potentially useful agents to improve this type of immunotherapy. Recently, Arnold et al ([14]) concluded that recombinant BCG has an enhanced immunostimulatory potential when compared to wild-type control BCG, and might offer new opportunities in the treatment of bladder cancer. With a low-dose treatment regimen for murine orthotopic bladder cancer, rBCG-IFNgamma significantly prolonged survival, whereas the therapeutic effect of wild-type control BCG, and might offer new opportunities in the treatment of bladder cancer.

In the treatment of superficial transitional cell carcinoma of the urinary bladder, Mitsumori et al ([15]) found that patients who received a high-dose epirubicin instillation had a significantly lower recurrence rate but the benefit of early instillation was not confirmed, as the study group was too small. In a study on 622 patients Kuroda et al. ([16]) concluded that the greatest effect of intravesical instillation of epirubicin after TUR-BT was shown by the regimen using the highest concentration (40mg/40ml) of the drug solution which was administered during a short period of time (4 months, 9doses, 360mg total dose).

Milonas et al ([17]) compared the efficacy of transurethral resection alone or transurethral resection followed by bladder instillations of Doxorubicin for 1 year in patients with superficial bladder carcinoma, and followed them long term for the incidence of recurrence and progression to muscle invasion. In regard to time of first recurrence and disease free survival this study indicated that adjuvant chemotherapy with Doxorubicin is superior to transurethral resection alone. However, progression in stage or recurrence rate was not influenced by the treatment regimen.

The combination of epirubicin and meglumine gammalinolenic acid have been found to be a logical choice of combination therapy for patients with superficial bladder carcinoma by Harris et al. ([18]). The efficacy of epirubicin was enhanced significantly when it was used in combination with most concentrations of MeGLA (< 300 microg/mL), and the two agents acted synergistically. There was a corresponding increase in epirubicin uptake by cells under these conditions. At high MeGLA concentrations, however, anthracycline solubility was compromised, and drug synergy was lost ([19]).

In order to prevent the relapse of bladder neoplasms, a 34 patients study ([20]) was designed to explore the effect of intravesical instillation of pirarubicin (THP) together with polyvinylpyrrolidone (PVP) on patients with superficial bladder cancer who had undergone surgical operation. Intravesical instillation of THP/PVP is effective for prevention of postoperative recurrence of superficial bladder cancer with fewer side effects. However, further study is needed for wide use in such way([21]). In the treatment of superficial bladder cancer, valrubicin, pirarubicin and gemcitabine are novelties. In a randomized trial conducted by Huang et al ([22]) the efficacy and side effects of intravesical mitoxantrone instillation with those of doxorubicin in superficial bladder cancer following transurethral resection, were compared. The instilled doses of doxorubicin and mitoxantrone were 30 and 14 mg, respectively. Thirty-three patients received mitoxantrone, whereas 30 patients used doxorubicin. The recurrence rate in the doxorubicin group was 30% (95% CI: 19.8%-38.8%), while it was 27.3% (95% CI: 17.5%-36.8%) in the mitoxantrone group. The median recurrence-free survival in the mitoxantrone group and in the doxorubicin group was 22 and 20 months, respectively (p=0.580). The results revealed that the efficacy and side effects of mitoxantrone were similar to those of doxorubicin. Especially for patients with pulmonary tuberculosis or aged patients with primary bladder tumors, mitoxantrone and doxorubicin may be the tolerable and effective intravesical agents([23]), endovesical thermochemotherapy appears to be more effective than standard endovesical chemotherapy as an adjuvant treatment for superficial bladder tumors at 24-month follow-up, despite an increased but acceptable local toxicity. The intravesical administration of mitomycin C could be safely performed in the form of both thermo-chemotherapy ([24]) and electromotive drug approach with an increased ablative success rate on small superficial tumor involving only minimal local side effects. In a multicentric
study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma (11) endovesical thermochemotherapy appeared to be more effective than standard endovesical chemotherapy as an adjuvant treatment for superficial bladder tumors at 24-month follow-up, despite an increased but acceptable local toxicity.

**CURRENT TREATMENTS OF MUSCLE-INVASIVE AND METASTATIC TRANSITIONAL CELL CARCINOMA (TCC)**

In the 1990s randomized controlled trials (RCT) of muscle-invasive and metastatic TCC focused on determining the efficacy of chemotherapy regimens combining cisplatin, vinblastine and methotrexate (CMV) or these drugs plus doxorubicin (MVAC). (12,13,14) Improvements in overall response rate, progression-free survival and survival were seen, but at the expense of increased toxicity, side-effects and toxic deaths.

Randomized controlled trials (RTI-s) in muscle-invasive and metastatic TCC reported this decade have focused on improving the effectiveness of MVAC by comparing it with combinations of gemcitabine-cisplatin, high dose intensity MVAC plus granulocyte-colony stimulating factor (G-CSF) and cisplatin plus 5-fluorouracil and alfa-interferon(15,16,17). Malmstrom et al. (18) found that neoadjuvant chemotherapy improves long-term survival after cystectomy in patients with stages T3 to T4a bladder carcinoma, while no survival benefit was found for stages T1 to T2 disease.Grossman et al. (19) concluded that as compared with radical cystectomy alone, the use of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin followed by radical cystectomy increases the likelihood of eliminating residual cancer in the cystectomy specimen and is associated with improved survival among patients with locally advanced bladder cancer. Millikan et al (20) found that there is an improved cure fraction by the combination of multiagent chemotherapy and surgery, although they found no preferred sequence. Importantly, it is possible to select appropriate patients for such therapy on the basis of clinical staging information. Freiha et al. (21) concluded that treatment with CMV (cisplatin, vinblastine and methotrexate) chemotherapy after radical cystectomy is an acceptable approach in patients with stages p3b and p4N0 or N1 transitional cell carcinoma of the bladder. Further studies must be performed to determine whether these results can be extrapolated to patients with more limited disease (stages p2 and p3a) who are currently treated with radical cystectomy or definitive irradiation (22).

Three cycles of neoadjuvant chemotherapy before cystectomy or radiotherapy did not give the 10% improvement in 3-year survival that was judged to be necessary for introduction into routine use. The chemotherapy regimen was associated with a higher pathological complete-response rate in primary tumours, but there was no clear evidence that it would increase survival (23). Neoadjuvant chemotherapy with cisplatin and methotrexate did not significantly improve disease-free or overall survival in 153 randomized patients with invasive bladder cancer(24). Two cycles of neoadjuvant methotrexate, cisplatin, and vinblastine (MCAV) chemotherapy were not shown to increase the rate of clinical complete response over that achieved with a standard induction therapy or to increase freedom from metastatic disease(25). M-VECA was found to be a safe and effective regimen for the treatment of patients with metastatic urothelial tumors (26). The results achieved in the 60 patients included in a study comparing the combination of carboplatin, methotrexate and vinblastine (M-CAVI) and M-VCAC indicated that M-CAVI is better tolerated than M-VCAC, although both treatment regimens had similar overall response rates, pathological response rates and survival in patients with locally advanced and locoregional bladder cancer(27). The combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has dominated chemotherapy for advanced bladder cancer for over 15 years. Randomized studies have shown (MVAC) superiority over cisplatin alone or in combination with cyclophosphamide and doxorubicin. However, (MVAC) exhibits a significant toxicity profile and achieves only a slight impact on overall survival. The combination of gemcitabine and cisplatin represents a new standard alternative of treatment for bladder cancer, based on a similar efficacy to and lower toxicity than the classic MVAC regimen. Future drug development will focus on the clinical usefulness of three-drug regimens (including gemcitabine, paclitaxel or docetaxel, and a platinum salt), and nonplatinum-based combinations. The regimen of gemcitabine and cisplatin has been found to be equally efficacious with less toxicity than methotrexate, vinblastine, doxorubicin, and cisplatin(MVAC). It has been adopted as the standard arm in a phase III trial for advanced bladder cancer, comparing it with the triplet of gemcitabine, paclitaxel, and cisplatin. Other active agents in bladder cancer include ifosfamide, carboplatin, docetaxel, and
A gemcitabine/cisplatin regimen has been shown to lead to comparable survival in a phase III comparison to methotrexate/vinblastine/doxorubicin/cisplatin in the metastatic setting with less toxicity (3). A number of additional doublet combinations have thus been investigated. Substitution of carboplatin for cisplatin is feasible but leads to an apparent lower complete response rate. A combination of doxorubicin and gemcitabine has been reported to lead to a 36% complete response rate (3). In addition to its antiproliferative and antiangiogenic effects, IFN-alpha has been shown to limit tumor invasion by restoring the normal balance between MMP-9 and E-cadherin and to enhance the activity of systemic chemotherapy (3).

Radiotherapy and concomitant 5-fluorouracil has been compared with radiotherapy alone in a prospective randomized study by Edland et al. (3). A prospective randomized phase III study based on neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder has been carried out by Martinez-Pineiro et al. (3). The survival rates were 48.6% for patients with pN0 disease, 37.5% for pN1 and 5% for pN2-4. Toxicity of cisplatin was minimal and there were no differences in perioperative morbidity between the arms (3). Some urinary bladder cancer tumors may respond favorable to Herceptin therapy (3). Based on the success seen with anti-HER2 monoclonal antibodies (Herceptin) and the promising results with epidermal growth factor receptor (EGFR) targeted agents (IMC-C225 Cetuximab, ZD1389 Iressa, OSI-774 Tarceva, GW 57016) in other tumor types, there is a great interest in assessing these agents in patients with bladder cancer (3). If this were true for bladder cancer, only 4/75 (5%) of G3 pT2 TCCs would be suitable for treatment (4). The role of trastuzumab, a humanized antibody to HER-2, in these tumours remains untested at present. However, specific treatments targeted toward oncogenes expressed in cancer cells are currently under development. Patients with urothelial carcinomas showing HER-2/ neu (human epidermal growth factor receptor 2) overexpression are candidates for such a specific treatment (trastuzumab) (4). Telomere ends are known to be shortened at every division of the cells. Telomerase is a ribonucleoprotein which compensate for the telomere ends and indispensable for the immortalization of the cells. Responses of transitional cell carcinoma of the bladder
(TCC) to commonly used chemotherapy agents such as mitomycin C (MMC), cisplatin and gemcitabine are often disappointing. The expression of human telomerase reverse transcriptase (hTERT) is associated with cellular aging and tumorigenesis. It was found in nearly all cancer types but not in most normal, somatic cells. Since human telomerase reverse transcriptase (hTERT) is tumor specifically expressed and contributes to the immortality and malignancy of the majority of tumors, it is regarded as a suitable antitumor target. It is reported that the enzyme is activated in a variety of cancer cells. Enhancement of cytotoxic drug effects on the growth of (TCC) cells by hTERT antisense AS- oligodeoxynucleotides ODNs allows a dose decrease in chemotherapy and confirms the suitability of hTERT as a target in a specific therapy approach. Specific hTERT inhibition causes remarkable short- and long-term effects on the growth of bladder cancer cells and represents a promising new treatment option of solid tumors. Kraemer et al. consider that this alternative treatment could be applied in terms of an instillation therapy. In solid tumor oncology, decisions regarding treatment are governed by histologic diagnosis. Despite this reliance on histology and the assumption that histology defines the disease, underlying molecular heterogeneity likely differentiates among patients’ outcomes. Betenski et al. concludes that molecular heterogeneity, if it confers different risks to patients and is unaccounted for in the design of a randomized study, can result in a clinical trial that is underpowered and fails to detect a truly effective new therapy for cancer. These authors feel that there is a need for individual approaches in the treatment of patients with bladder cancer, and we strongly agree with them. The study of Yang et al. supports intratumoral vaccination as a strategy for immunotherapy of established tumors. Keyhole limpet hemocyanin (KLH) is a high-molecular-weight copper-containing respiratory protein antigen collected from the haemolymph of the sea mollusk Megathura crenulata, a non-specific immunomodulator, that induces both a cell-mediated and a humoral response. KLH has demonstrated efficacy and has induced long-term remissions against carcinoma in situ (CIS) in a limited number of cases. However, most patients with CIS progressed over time whatever the substance instilled, whether KLH or BCG.

Bropirimine is an orally-active immunostimulant that has an antitumor effect on superficial transitional cell carcinoma of the bladder. Bacteria such as Salmonella and Listeria can be attenuated by genetically-defined mutations and provide effective vehicles for DNA vaccines encoding tumor-associated antigens. Salmonella and nonpathogenic strains of Clostridium can selectively accumulate in tumors in vivo, providing attractive delivery systems to target immunomodulatory molecules and therapeutic agents to the tumor site.

RESULTS

(VAX - x, DRUG - x)- Couples

We define the combination of a specific cancer drug (DRUG - x) and its pre-administrated , corresponding , autologous cancer vaccine (VAX-x), made of dead/killed cancer cells from the patient, and bearing on their genome the mutations that would be induced into these cancer cells by the specific drug (DRUG - x), as a (VAX - x, DRUG - x)- couple, clearly indicating that the autologous (therapeutic) cancer vaccine, VAX - x, is pre-administrated to its corresponding DRUG - x couple-partner.

(VAX - x, DRUG - x)- Couples are formed by :

1. a currently used anticancer drug (or a combination of anticancer drugs) - termed (DRUG-x),
2. a specific, anti-cancer, autologous vaccine, VAX-x, made of dead/killed cancer cells (or cancer cells parts/subunits), prelevated from the patient and bearing on their genome/biochemical structure the mutations that would be induced into these cancer cells by the following, to come anticancer drug, or anticancer drugs combination.

The role of a VAX-x , within a (VAX - x, DRUG - x)-couple, would be to prevent the emergence of DRUG-x - resistant cancer cells, whereas the role of DRUG-x would be to kill DRUG-x-sensitive cancer cells in order to cure bladder cancer in particular, and any other type of cancer in general.

Our innovative idea to introduce (VAX - x, DRUG - x)- Couples as a completely new treatment approach for superficial, muscle-invasive, and metastatic transitional cell carcinoma (TCC) of the bladder, was inspired and originates from our earlier theoretical research studies in the field of HIV-1(3). The Immune Response Corporation (Nasdaq: IMNR), a biopharmaceutical company dedicated to becoming a leading immune-based therapy company in HIV, has based
its activity on its patented whole-killed virus technology, co-invented by Company founder Dr. Jonas Salk, to stimulate HIV immune responses. REMUNE® (((52a))), currently in Phase II clinical trials, is being developed as a first-line treatment for people with early-stage HIV and might be used as a non-specific anti-cancer vaccine in the treatment of superficial bladder cancer. Other interesting anti HIV-1 vaccines / therapeutic vaccines have been produced by Therion Biologies Corporation (((52b))) - based on the HIV-1 env/gag/pol genes (TBC-3B) and MN r- gp120/HIV-1 in alum., Apollon, Inc. - an HIV-1 gag-pol DNA Vaccine (APL-400-047) and ADVENTRX Pharmaceuticals (((52c))) who developed EradicAide, an HIV therapeutic vaccine, composed of six synthetic peptides, which stimulate a killer T-cell response to clear HIV-infected cells. A unique feature of this treatment is that it is designed to not elicit an antibody response. It is antibody-negative.

All these anti-HIV-1 vaccines / therapeutic-vaccines may be used as non-specific anti-cancer vaccines in the treatment of superficial bladder cancer, in a way similar to BCG.

Affymetrix (((53)), a leading US company in DNA-chip technology has developed GeneChip oligonucleotide probe arrays that are manufactured using a high resolution photolithographic fabrication process adapted from the semiconductor industry, for HIV-1 mutations determinations. This high-tech company has probably also the technical and scientific capacity to determine the specific mutations which cancer drugs (((54))) induce into cancer cells, or on certain cancer - cell parts/subunits which can be found only in cancer cells and cannot be found in normal human cells. In this way, the VAX-x component of (VAX - x, DRUG - x)- couples may be standardized and produced in large scale by the bio-pharmaceutical industry.

The review of Coulie (((55))) has been focused on the identification of several tumour antigens, their molecular nature, and how they can be used to develop anti-cancer vaccines.

Anti-cancer vaccines are normally used only as a treatment, after the cancer has been found in a patient. Anti - cancer vaccines (VAX-x) can be made from the person's own cancer cells (i.e. autologous vaccine - meaning that the antigens are derived from the same individual they are used to treat.). The cancer cells are treated with heat or radiation, so that they cannot multiply and grow, and to make sure that they cannot cause harm. While the cells are dead, the antigens are still recognized by the the immune system, which responds by attacking the dead cells. The immune system will also attack the live cancer cells carrying the antigen that was displayed on the dead cells. Autologous anti-cancer vaccines in development include those utilizing whole cells, tumor lysates, RNA or heat shock proteins.

Early attempts at autologous cancer vaccines involved whole cell preparations or lysates of a patient's tumor, which were shown to be unsuccessful, as unpurified cellular contents send both stimulatory and suppressive immune signals.

Let us now suppose that the person's cancer cells are exposed, in vitro, to all currently existing and currently approved cancer drugs (((56))) in order to assess the most appropriate treatment for the respective person. Some anti-cancer drugs will surely prove to be more efficient and effective than others in killing cancer cells, but in vitro results do not necessarily correlate with in vivo results. For most, if not for all cancer drugs (((57)), drug -resistant cancer cells may select naturally or may be grown by adaptive techniques in which the cancer cells are exposed to increasing doses of a certain cytostatic (Drug-x). These one-drug (naturally) resistant cancer cells can now be killed with heat or radiation, so that they preserve the exact mutations induced into their genomic/biochemic structure by the respective one-drug (DRUG-x), and can be used as the VAX-x component of a (VAX - x, DRUG - x)- Couple.

VAX - x should be administrated before DRUG-x in order to allow the immune system to develop an immune response against DRUG-x resistant cancer cells before they even get the chance to arise. As soon as a good immune response to these in - vitro heat - or -radiation - killed (IVHRK) DRUG-x resistant cancer cells is recorded, the treatment with DRUG-x can commence. The sinergetic effect of VAX-x followed by DRUG-x acts like a scissor on that person's cancer cells and may eradicate all of them. Successive series of different (VAX - x, DRUG - x)- couples may ultimately lead to eradication of high stage and even metastatic cancer. Another advantage of (VAX - x, DRUG - x)- couples over conventional chemotherapy (e.g. MVAC) is the fact that successive one drug couples can be designed, which are less toxic (e.g. (VAX - 1, methotrexate), -----> (VAX - 2, vinblastine), -----> (VAX - 3, doxorubicin)------> (VAX - 4, cisplatin)

This series may also be followed by other monodrug-couples, by 2- and 3- drug combination based couples, and
even by a 4 drugs based couple (VAX - x, MVAC)

Alternatively, certain proteins may be taken from the cancer cells and used to make a cancer vaccine. These include antigens (the proteins on the cell surface which can stimulate an immune response). Unique antigens are antigens that occur only in cancer cells and do not exist in normal tissues. They arise from mutations that occur as the tumor cells grow. The vast majority of unique antigens are not only specific to cancer cells but also specific to each individual patient. Antigen vaccines use tumor-specific antigens -- proteins displayed on a tumor cell -- to stimulate the immune system. By injecting these antigens into the cancerous area of the patient, the immune system will produce an increased amount of antibodies or cytotoxic T lymphocytes, also known as killer T cells, to attack cancer cells that carry that specific antigen.

Heat shock proteins (HSPs) are believed to play a role in the presentation of antigens on the cell surface to help the immune system recognize diseased cells and therefore they can be conveniently used as potential anti-cancer vaccines. Also the entire repertoire of unique antigens from an individual patient's tumor can be used to stimulate a strong tumor-specific immune response. And again the entire repertoire of antigens unique to a person's cancer cells can be exposed to each FDA-approved cancer drug (55) and drug induced mutations on the biochemical structure may be recorded (55). DRUG - x modified antigens from an individual patient's tumor can then be used as the VAX-x component of a (VAX - x, DRUG - x)-Couple.

Dendritic cells break the antigens on the cancer cell surfaces into smaller pieces. The dendritic cells then display those antigen pieces to the killer T cells. To make a dendritic cell vaccine, some of the patient's dendritic cells are extracted and immune cell stimulants are used to reproduce large amounts of dendritic cells in the lab. These dendritic cells are then exposed to antigens from the patient's cancer cells. This combination of dendritic cells and antigens is then injected into the patient, and works like an anti-cancer vaccine. By analogy dendritic cells and DRUG - x exposed antigens can be injected into a patient as a VAX - x component of a (VAX - x, DRUG - x)-Couple.

Telomerase, a protein found in all major human cancers has proven to stimulate immune cells which are then able to kill multiple cancer cells and slow tumor growth. Almost all cancers express the telomerase protein. Thus telomerase might form the basis of a possible universal cancer vaccine. The TERT vaccine, made of a certain part of the telomerase protein, was able to stimulate an immune response that killed a wide variety of cancer cells and it showed that it could slow the growth of melanoma, bladder and breast cancers implanted into genetically unrelated mice. No other vaccine has been able to induce such a broad immune response. However, an effective anti-cancer vaccine has to display the antigens exactly as the cancer cells do. The effects of all FDA-approved anti-cancer drugs (55) on the biochemical structure of telomerase should be studied. Since telomerase may constitute the main component of an universal anti-cancer vaccine, it should be administrated as the main and sole component of VAX - x in a DRUG-x-modified formula within (VAX - x, DRUG - x)- couples, and in its pristine, original, unmodified biochemical formula at the end of all successive (VAX - x, DRUG - x)- couples treatments, as a final vaccine sealing the victory of combined vaccine and chemotherapy science over cancer.

Farmarubicin-exposed telomerase (TERT-farmarubicin) should be used as the VAX-x component within the (TERT-farmarubicin, FARMARUBICIN) - couple in order to treat superficial bladder cancer. Other (VAX - x, DRUG - x)-couples suitable to treat superficial bladder cancer would be e.g. (TERT-thiotepa, THIOTEPA), (TERT-doxorubicin, DOXORUBICIN), (TERT-mitomycin, MITOMYCIN). Accordingly, a successive series of 4 couples may be employed to replace MVAC chemotherapy in the treatment of muscle-invasive and metastatic bladder cancer: (TERT-methotrexate, METHOTREXATE), ---->(TERT-vinblastine, VINBLASTINE), ---->(TERT-doxorubicin, DOXORUBICIN), -----> (TERT-cisplatin, CISPLATIN).

At a limit , a powerful (TERT-MVAC, MVAC)-couple should be ultimately considered for the eradication of high stage and/or metastatic bladder cancers.

**CONCLUSIONS**

(VAX - x, DRUG - x)- Couples may be used in the treatment of all bladder cancers in particular, as well as in the treatment of all other types of cancer. This new strategy, theory and practical solution to treat cancer patients speaks for the individualization of anti-cancer treatments, rather than for large randomized clinical trials (RCT-s), since the patient's own cancer cells are used as a therapeutic vaccine. The main advantages of (VAX - x, DRUG - x)- Couples, when compared to conventional standard chemotherapy (e.g. MVAC) consist in the following:
1. higher efficiency in eradicating cancer in any patient, due to the sinergy between VAX - x, the immune system and DRUG - x;

2. much lower toxicity and fewer side effects, since anti-cancer drugs can be administered in monotherapy, doublets and triplets, compared to the 4-drug MVAC-therapy. The administration of successive (VAX - x, DRUG - x)-Couples, each based on a one-drug DRUG-x component, being also possible.

3. the use of (VAX - x, DRUG - x)- Couples creates an anti-cancer sinergy between the VAX - x vaccine, the patient's immune system, and the employed anticancer drugs, and this sinergetical effect is decisive in the eradication of cancer.

(VAX - x, DRUG - x)- couples may prove to be able to cure superficial, muscle-invasive, and even metastatic transitional cell carcinomas(TCC-s) of the bladder, especially those(TCC-s) which are refractory to current standard treatments and to all other existing alternative treatments. In addition, (VAX - x, DRUG - x)- couples may also prove to be more efficient in curing advanced and even metastatic cancers and to be less toxic than current conventional therapies, having the potential to become the standard treatment of care and cure for all bladder cancers, for all other types of cancer, and for absolutely all infectious diseases.

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Author Information

Iosif Secasan
Department of Urologic Surgery, Spitalul Judetean Resita / The Hospital of Resita

Dan I. Pop
Data International SRL

Ciprian C. Secasan
Department of Microbiology / Department of Urologic Surgery, Spitalul Judetean Resita / The Hospital of Resita