

# THE CANCER REVOLUTION

## **Additional Material for Appendix 1**

**Prof. Shimon Slavin**

*Prof. Slavin provided us with wxtensive material on his work that we unfortunately were not able to include in its entirety. Here we are providing the full, original, unedited material.*

### **Treatment of cancer at International Center for Cell Therapy & Cancer Immunotherapy (CTCI)**

Here are some general principles of some of our treatment strategies for your consideration, which you are welcome to share with the treating oncologist and he/she is welcome to contact me in case there will be a need for better understanding of any of the procedures available at our centre or if there will be a need for further explanation of the procedures which are not available elsewhere.

As you may understand, I cannot give specific recommendations for a complicated patient with cancer without revising a fully updated medical report. In many cases, I need to see the patient before submitting final recommendations, especially if the patient has a long history of resistant or recurrent metastatic disease. As I am sure you realise, treating cancer is like shooting a moving target, so treatment may have to be changed depending on the disease status and patient's general condition. This is especially relevant for procedures that may be recommended at our centre, the International Centre for Cell Therapy & Cancer Immunotherapy (CTCI), because we believe in fully personalised medicine. There are no two cancers that are the same and there are no two individuals that are the same, and therefore, there is no reason why treatment should be the same for all patients with the same disease.

For your information, we are now in the process of clinical application of innovative modalities for treatment of cancer, all types of cancer included, focusing on targeted and cell-mediated immunotherapy including vaccines, oncolytic viruses and especially using cancer killer cells (T cells, NK cells & macrophages) stem cells-based anti-cancer modalities and other personalised tumour-targeted approaches for the treatment of patients with cancer at a clinical stage known to be resistant to conventional anti-cancer modalities or at risk of tumour recurrence following conventional anti-cancer modalities.

Obviously, we prefer to treat cancer at an early stage of the disease, preferably as soon as diagnosis is done, because then optimal treatment can be planned and tumour sample cryopreserved from biopsy and even more generously from surgical preparation in patients undergoing surgical removal of the primary malignancy. At the stage of minimal residual disease following initial tumour debulking cure can be accomplished by combining conventional treatment with treatment of minimal residual disease by targeted immunotherapy, even for patients at high risk of recurrent disease, unlikely to be cured by any of the conventional anti-cancer agents. Most patients with cancer, reach a stage of minimal residual disease following initial debulking by surgery or first line chemotherapy or radiation therapy if indicted or following additional anti-cancer modalities. At present, when no tumour is visible, oncologists tend to send such patients away with no further treatment recommendations. Yet, every cancer starts with a single cell. When such an abnormal cell escapes the surveillance of the immune system, continuous division results in tumour progression. At a stage of one million cells, the size of the cancer lesion is the size of a head of a pin. No technology can detect such small cancer lesions. Therefore,

patients may have many such small lesions in different locations, yet, such patients may be considered fully cured. Tumour progression may occur at a later date. Our goal and patient's best chance, sometimes the only chance, to be cured is to be treated at the stage of minimal residual disease.

Unfortunately, most patients seek for help only when tumour metastases are diagnosed, when all other measures fail, when it may be difficult or impossible to minimise the tumour burden due to multi-drug resistance. Unfortunately, when cancer metastases progress, and when malignant cells are no longer responsive to available anti-cancer modalities, there is no real option for cure with any of the conventional anti-cancer agents, yet, we are willing to try and slow or stop the disease process, on a fully personalised basis using unique procedures available at our clinic at CTCI. Although we will be happy to treat any patient in need and offer several rational and most innovative therapeutic approaches trying to control the disease, yet, we can never promise successful outcome.

Another important principle that should be taken into consideration is that we always recommend using as many non-cross resistant anti-cancer procedures as possible, each operating against a different target on resistant cancer cells, such as if cancer cells become resistant against a particular treatment, which they always do, and escape one type of anti-cancer treatment, a subsequent treatment based on another principle will be applied in an attempt to kill or block replication of such cells by a method that that operates through a different anti-cancer mechanism. The number of anti-cancer procedures that can be applied depend in part on the phenotype and available targets on cancer cells, the period of time a patient can stay in Tel Aviv and also considering financial restrictions among other factors that may vary between patient to patient.

Since every anti-cancer treatment is likely to be much more effective against minimal residual disease, our goal is to apply a two step approach: [1] First trying to eliminate as many cancer cells as possible, preferably if still possible, down to the stage of minimal residual disease; [2] apply innovative anti-cancer modalities focusing on immunotherapy in an attempt to control residual malignant cells even if complete elimination cannot be accomplished. After all, if we can keep the number of malignant cells fixed under balance and prevent or minimise tumour progression, patients may live long and even remain asymptomatic. In most cases, the danger is not from the number of tumour cells at present, but rather from tumour progression that is anticipated in the future if treatment fails.

It should be realised that our treatment program has to be regarded as an experimental approach, not yet considered standard of care. To avoid false hopes it must be clear that we cannot promise cure or successful control of the disease, although we are committed to do our best to try and accomplish such a goal. Considering the experimental nature of our treatment program, we always recommend to apply our "out of the box" treatment in addition to, rather than instead of conventional treatment in order to be sure that maximal possible treatment was administered by combining conventional treatment with experimental treatment, rather than replacing conventional protocol with experimental protocol. However, in this case it seems all conventional methods were already applied and failed, thus justifying clinical application of innovative procedures.

For your information, the two-step approach consists of the following procedures:

### **[1] Optimal tumour debulking before attempting the use of immunotherapy**

Unfortunately, despite the use of all available anti-cancer modalities elimination of all malignant cells and prevention of tumour progression or recurrence may not be accomplished because of 2 main reasons. First, the primary lesion may be located in an

inoperable location and/or may be invasive such as residual malignant cells may be invisible to the surgeon; second, may be due to the fact that the cancer initiating cells, the so-called cancer stem cells, are a priori resistant to chemotherapy and radiation. Based on the above, we recommend additional treatment in an attempt to try and further reduce the number of residual malignant cells based on the use of new methods and new devices: Oncothermia on the one hand and well-tolerated liposomal chemotherapy on the other.

The principles of oncothermia are based on induction of modulated deep radio-frequency electro-hyperthermia, with an increase of the temperature over the cell wall of malignant cells together with induction of direct electric-field energy absorption in the extracellular liquid towards destroying the membrane of the cancer cells. The anti-cancer effects of oncothermia can be synergic with concomitant treatment with radiotherapy and chemotherapeutic agents.

Oncothermia acts selectively or preferentially against malignant cells via the higher conductivity and higher permittivity of the extracellular matrix of malignant tissue, resulting in selectivity of killing of malignant cells by apoptosis that can be enhanced by local delivery of anti-cancer chemotherapy, especially anti-cancer agents provided as liposomes.

Using our new Oncothermia device, we can provide Oncothermic Non-invasive Extracorporeal Targeted anti-cancer therapy (OncoNET), which represents a very safe and painless treatment of cancer. Oncothermia damages preferentially the cell wall of malignant cells and afferent blood vessels supporting cancer metastases. When oncothermia is combined with sub-toxic anti-cancer agents administered systemically, a much more effective tumour dose can be delivered directly into the cancer cells, due to the selective thermic effect over the membrane of the cancer cell that may become much more permeable. The selective effect of oncothermia on cancer cells results from their enhanced metabolism as compared with adjacent normal cells. When active anti-cancer agent is entrapped in liposomes release of the active ingredient can be delivered into the malignant tissue as it is being released locally by the non-ionising low radiofrequency energy concentration that targets the membrane of malignant cells with temperature gradient, resulting in dispersion of the cell membrane proteins and better penetration of the anti-cancer agent at high local concentration into the malignant cells. As such, the malignant cells may die as a result of apoptosis or the cytotoxic effect of chemotherapy.

Taken together, the anti-cancer effects supported by OncoNET may thus be enhanced by: (1) high local delivery of anti-cancer chemotherapy administered systemically at low and well tolerated doses that under Oncothermia may be released at much more effective concentrations selectively into the malignant cells; (2) enhanced perfusion of the malignant tissue due to dilatation of the blood vessels nourishing the primary tumour or tumour metastases induced by hyperthermia; (3) increased permeability of the active anti-cancer ingredients administered prior to exposure of the patient to Oncothermia due to disruption of the cell membrane of the malignant cells damaged by oncothermia, thus potentially even overcome drug resistance; (4) potential enhancement of anti-cancer immunotherapy by exposure of the contents of the malignant cells released into the circulation to the immune system in parallel with activation of the immune system on the one hand, and neutralisation of inhibitors of anti-cancer immunity by metronomic treatment, on the other.

The other apparatus that may help increasing the concentration of chemotherapy and anti-cancer killer cells in the malignant tissue consists of low energy acoustic shockwave device using a procedure we name acoustic shockwave therapy (AST). Short-term

exposure of tissues to AST results in dilatation of blood vessels and increased blood flow into the cancer lesion. Transient increased perfusion of the primary tumour or metastatic lesions following exposure to oncothermia may also increase the permeability of the cancer cell wall to chemotherapy, thus possibly overcoming the multi-drug resistance that protects cancer cells from conventional chemotherapy. In addition, as will be detailed below, transient increased perfusion of cancer lesions by AST may allow increased flow of activated cancer killer cells (T cells, NK cells and macrophages) into the cancer lesions is likely to increase their therapeutic effects. In addition, the combined damage of visible cancer lesions attacked by a combination of oncothermia and AST may result in release of intra-cellular tumour antigens to the circulation, thus allowing the immune system to react against otherwise “invisible” tumour antigens. Subsequently, the use anti-angiogenic treatment is recommended in an attempt to shut off the blood supply and source of energy to rapidly proliferating cancer cells. The abnormal blood vessels supporting the primary tumour or the growing metastases may also be damaged later on by the combination of oncothermia, AST and chemotherapy, thus inducing a secondary anti-angiogenic effects to minimise blood supply to the growing metastases.

At present, we recommend using a most effective preparation of anti-cancer liposomal nanoparticles - Lipoplatin (liposomal Cisplatin) - not yet available in the market, in conjunction with oncothermia and AST. Lipoplatin can provide a most remarkable anti-cancer effects with a very safe pharmaceutical profile based on increased permeability of the cancer vasculature and cancer cell membrane because the active ingredient, cisplatin, is apparently one of the most effective anti-cancer chemotherapy that exist.

We believe that the combination of targeted oncothermia, AST and chemotherapy, especially focusing on Lipoplatin, will provide each patient in need the best chance for optimal tumour debulking despite resistance to available anti-cancer agents. Once we can minimise the number of chemotherapy-resistant malignant cells, other methods focusing on immunotherapy using methods listed below are likely to have a better chance to eliminate or control the rate of progression of residual malignant cells, including perhaps the fully resistant cancer stem cells that may be responsible for tumour recurrence in patients considered “cured” because of lack of visible residual disease.

## **[2] Treatment of minimal residual disease**

As soon as the patient exploited all possible approaches for minimising the tumour burden, as described in [1] above, innovative procedures described in this section will be recommended focusing on targeted anti-cancer therapy as well as using the immune system to fight cancer. As will be detailed below, immunotherapy will be based on an attempt to activate patient’s own immune system cells against his own malignant cells on the one hand, while using foreign (allogeneic) immune system cells, allogeneic lymphocytes, to kill cancer cells simply because patient’s own cells may fail to do so, on the other.

Procedures that preferably should include combination of anti-cancer modalities as indicated, to minimise escape of cancer cells developing resistance to conventional treatment may include some of the following experimental procedures:

- Conventional or special agents with specific reactivity against patient’s malignant cells (e.g. monoclonal or bispecific antibodies against cancer antigens; biologic response modifiers and various inhibitors of cell signals involved in activation of cancer cells; treatment against viruses that may induce cancer or associated with cancer; agents that interfere with metabolic activities of the malignant cells, etc.).

- Combinatorial anti-cancer therapy (COMBAT). COMBAT at our center consists of low-dose anticancer agent (Cytosan) to suppress regulatory T cells, anti-inflammatory, pro-apoptotic and anti-angiogenic agents to minimise growth of cancer cells.
- Newer agents are now used to release patient's immune system from negative control by suppressor cells of the immune system (e.g. anti-CTLA4; and PD1).
- Using autologous (patient's own) tumour cell vaccines prepared from cryopreserved cancer cells that patient should insist getting from the surgeon following surgical removal of cancer lesions. Alternatively, vaccine could be prepared from allogeneic (foreign) cancer cells matched as much as possible with patients tissue antigens. If no cryopreserved cancer tissue is available tumour antigens may be prepared from patients serum or other fluids resulting from cancer (ascites or pleural effusion). Sometimes the tumour itself or tumour metastases can be injected with agents that will turn the tumour lesion as an internal vaccine.
- Additional approaches to activate the patient's own immune system against cancer,
- including interleukin 2 (IL-2), and interferon that activate T-cells and natural killer cells.
- More recently we are using methods for activation of natural killer T cells and new non-toxic, well-tolerated biologic agent (GcMAF) that activates the patient's own macrophage system.
- Activation of the patient's immune system may also be attempted by using mixed bacterial toxins, a long established approach, also know as Coley's toxins.
- Intentionally mismatched killer cells, allogeneic lymphocytes activated in the
- laboratory with interleukin 2 (IL-2) can be used for effective "rejection" of residual malignant cells resistant to chemotherapy. Continuous activation of allogeneic killer cells in the patient's body can be accomplished by administration of IL-2 for 5 days, while allogeneic lymphocytes circulate before being rejected.
- Systemic or intratumoural administration of harmless cancer-seeking viruses (oncolytic viruses) that can penetrate into the malignant cells and destroy them or induce an immune response against the cancer cells modified by viral antigens.
- For patients with bone metastases (e.g. patients with prostate cancer, breast cancer etc.) additional treatment with Zometa (zoledronic acid), which may also improve anti-cancer immunity.
- For patients with bulky yet responsive disease, we may consider more aggressive treatment, based on the use of high-dose chemotherapy supported by autologous stem cell transplantation followed by immunotherapy to eliminate minimal residual disease.

As you can see from the above, we have many experimental treatment options available and will be happy to offer treatment that focuses on immunotherapy, in an attempt to improve the outcome by slowing disease progression by interacting against malignant cells that may no longer respond to conventional treatment. Yet, it should be remembered that although we promise to try as much as we can, we can never promise a cure, although we certainly will do our best to try and reach this goal by clinical application of a combination of procedures that may complement each other on a personalised basis.

Since our approach is personalised, administered on a compassionate basis, rather than done as a formal study, we need to characterise the details of each tumour and have all details about each patient, because our approach is both tumour-specific and patient-specific. These requirements result in back and forth inter-communication by emails,

phone calls, mails for evaluation of disease status and patient's general condition and this process is time consuming.