Final Report Summary - CTCTRAP (Circulating Tumor Cells TheRapeutic APheresis: a novel biotechnology enabling personalized therapy for all cancer patients)

Executive Summary:
Chemotherapy is slowly being supplemented by a new generation of drugs that recognize specific targets in or on cancer cells and has proven to be more effective with markedly fewer side effects. During the course of the disease alternative oncogenic signaling pathways take over inevitably leading to drug resistance. As a consequence renewed tumor analysis is required to redefine the optimal treatment regiment. However a biopsy can frequently not be obtained without risk and / or discomfort to the patient. Circulating tumor cells (CTC) may circumvent this problem. CTC refer to cells that detach from a primary tumor or metastatic site, circulate in the peripheral blood and may form metastasis. CTC represent a "liquid biopsy" that can be used to tailor treatment for individual patients. CTC are however rare and can only be obtained for further characterization in a small fraction of patients.

In the CTCTrap consortium universities, research institutions and SMEs have explored various ways to isolate CTC from 1-2 liters of blood. The approach ultimately evaluated in cancer patients was Diagnostic LeukApheresis (DLA) in combination with the FDA cleared CellSearch system targeting EpCAM+ CTC and technology based on differences in physical characteristics between blood cells and cancer cells (EpCAM- CTC). This approach has led to a significant increase in the number of isolated CTC enabling a more comprehensive real-time characterization of the cancer. Development is however still ongoing to further improve the CTC enrichment in conjunction with DLA.

Using the technology developed in CTCTrap EpCAM+ as well EpCAM- CTC were identified in both prostate as well as breast cancer patients. Long-term follow-up will be needed to determine the relation with clinical outcome. Efforts are still ongoing to gather new knowledge on the differences at both the molecular and protein level of these CTC. These results will provide insight in the mechanism of metastasis, provide a risk assessment and guide the optimal therapy choice for the patients. Pilot work on the health economic consequences of the use of CTC’s in cancer disease management has been conducted. Although the value of diagnostics generally is appreciated, the current incentive structures do not facilitate nor reward innovation in diagnostic testing. Diagnostic testing is seen as part of the value created by drugs and current reimbursement schemes do not easily incentivize further developments nor implementation of diagnostics. For this reason, it is very useful to anticipate market access and reimbursement in case of advanced molecular diagnostics, such as developed in the CTCTrap program.

Project Context and Objectives:
The overall aim of the CTCTrap program was to develop technology that enabled the isolation of CTC in all cancer patients with disseminated disease and characterize these tumor cells to help guide the choice of the optimal therapy. In addition the health economic consequences of CTC as a liquid biopsy were evaluated. In the CTCTrap program nine work packages were defined. The objective of work package 1 was to develop technology to isolate CTC from large blood volumes (1-2 Liters). The objective of work package 2 was to develop technology that enabled the detection of CTC in the blood discarded by the CellSearch system (EpCAM- CTC). In work package 3 tools and protocols were to be developed that enabled the molecular characterization of individual CTC. In work package 4 the reagents and protocols needed to be developed to enable the identification of the CTC in the enriched cell suspensions obtained from work package 1 and 2. The objective of work package
5 was to develop the data analysis tools to analyze the data gathered from the CTC characterizations. Work package 6 aimed to develop mouse models in which the CTC could be expanded to facilitate the ability to test the best treatment choice for the patient. In work package 7 the tools and protocols developed in WP1, 2, 3, 4, 5 and 6 were to be tested and evaluated on breast and prostate cancer patients. The objective of work package 8 was to start to evaluate the health economic consequences of the use of CTC’s in cancer disease management and the management of the consortium resided in work package 9.

Project Results:

Work package 1: The original plan was to develop a Therapeutic Apheresis (TA) column, to capture CTC from peripheral blood of cancer patients and then reintroduce the blood devoid of tumor to the blood of the patient. After evaluation of the TA columns the enrichment of the tumor cells was not sufficient to proceed to actual patients. Alternative CTC enrichment strategies were developed using Diagnostic LeukaApheresis (DLA) through which mononuclear cell fractions from 1-2 liters of blood were obtained. After protocols were established DLAs were performed and CTC isolated according to the Standard Operating procedures developed in CTCTrap program from 30 metastatic breast and prostate cancer patients at UDUS, IOV, IGR, ICR and the UT. The number of CTC obtained through DLA was indeed substantially larger as that could be obtained from 7.5 ml of blood. The recovery percentage however was relatively low leading to various approaches with which the recovery was increased. The program will now continue in the EU IMI program CANCER-ID.

Work package 2: Tools and protocols to isolate and characterize CTC not captured by the CellSearch system were developed and validated at the clinical sites with blood from healthy donors spiked with cells derived from tumor derived cell lines. Spiking experiments showed that the tools and protocols could be executed well at each site with an overall recovery of 40%. Fate of the 60% of spiked cells that were not recovered is not identified yet. The use of the tools and protocols were tested on blood from 29 metastatic breast and 72 metastatic prostate cancer patients. In blood from these patients both EpCAM+, CK+, CD45- and EpCAM-, CK+, CD45- nucleated cells were identified. Molecular proof that these cells are indeed cancer cells and whether or not their presence is associated with a worse prognosis will still need to be obtained.

Work package 3: In this work package tools and protocols were developed to isolate single CTC cell and amplify the DNA in these samples for molecular profiling by either array CGH or sequencing. The protocols have been made available on the CTCTrap website for use by the general public. A major part of this work has been performed in work package 5 and a more detailed description can be found in the WP5 description.

Work package 4: The main aim of this work package was to develop protocols and reagents to identify and characterize CTC from CTC enriched blood samples. The reagents and protocols were successfully developed and evaluated in a validation study using blood samples spiked with tumor cells and blood samples from metastatic cancer patients. Some of the reagents could be provided by Aczon whereas others were obtained from commercial sources. The protocols have been made available on the CTCTrap website for use by the general public.

Work package 5: Although data basis were developed to enter information gathered during the project most of the effort has been dedicated to extract, amplify and analyze the DNA contained in single CTC. In addition to improve the identification of CTC among the fluorescently labeled cells images an image analysis program is being developed. To arrive at a common definition of a CTC an Open Source image analysis program is being developed in a joint effort between the IMI program CANCER-ID and the FP7 program CTCTrap. The first version of this ACCEPT program is currently being evaluated by the consortium members and will be made available to the public through the CTCTrap website.

Work package 6: The main aim of this work package was the development of animal models to expand CTC derived from prostate and breast cancer patients. In-vitro and in-vivo models were successfully developed and CTC derived from DLA’s from prostate cancer patients were used in these models. These human CTC might survive in the circulation and the hematopoietic compartment of immunodeficient NSG mice, however, they do not seem to be tumorigenic in the developed experimental setup.

Work package 7: A validation study conducted across the clinical sites demonstrated that the tools and protocols developed in the CTCTrap program could be executed well. Enumeration of CTC in 101 metastatic cancer patients showed the presence of EpCAM+ as well as EpCAM- CTC. Implications of these findings are still being investigated. Processing of large blood volumes
by means of tools and protocols developed in the CTCTrap program showed a significant increase of the number of CTC that could be isolated in all 30 cancer patients subjected to the procedure.

Work package 8: This work package aims to do some pilot work on the health economic consequences of the use of CTC’s in cancer management in general, and more specifically the CTCTrap development. Although the value of diagnostics generally is appreciated, the current incentive structures do not facilitate nor reward innovation in diagnostic testing. Diagnostic testing is seen as part of the value created by drugs and current reimbursement schemes do not easily incentivize further developments nor implementation of diagnostics. For this reason, it is very useful to anticipate market access and reimbursement in case of advanced molecular diagnostics, such as developed in CTCTrap.

The detailed reports provide insight into some of the specific challenges, i.e. (1) how can we determine health economic impact in case of limited or missing clinical evidence and (2) can we use standard state-transition models for the health economic evaluation of personalized medicine (case prostate cancer). In two studies more detail, is provided and a model introduced for the use of CTCs to detect early metastases for tailoring treatment strategies in breast cancer and for switching therapies in metastatic prostate cancer. These studies are complemented with an overview of the stakeholder input regarding the requirements for further development and implementation of CTCTrap.

Work package 9: Project management, the final scientific and commercial report and the financial status reports from each of the participants are placed on Participant Portal (https://webgate.ec.europa.eu/cas/login). The CTCTrap website (http://www.utwente.nl/tnw/ctctrap/) is used for dissemination of the results of CTCTrap and contains a description of the tools and protocols developed in the CTCTrap program that can be accessed to all interested parties. Within the website a secure site only accessible for the members that signed the consortium agreement is available to allow share more detailed and confidential information. The seventh e-newsletter has been generated, placed on the CTCTrap website and distributed to the communication departments of each of the partners.

Potential Impact:

The potential impact of the CTCTrap proposal on the cancer treatment is expected to be relevant for:

1. Containment of Health System Costs:
Cancer treatments are incredibly expensive and they will become an enormous economic burden for the EU if the efficiency of cancer therapy will not be improved. Increasing the access to personalized cancer treatments aims at addressing this issue. The impact of CTCTrap is the development of new and better tests to identify patients eligible for adjuvant treatment and select the appropriate therapy.

2. Impact on patient’s life:
Side effects of cancer treatment are very often so oppressive that they cease to create a benefit for the patient. The tremendous decrease in quality of life is not counterbalanced by the effectiveness of the treatment. Appropriate testing and correctly classifying patients will lead to gains in quality of life and quality adjusted life years (QALYs).

The impact of CTCTrap is the development of better tests to differentiate between symptoms caused by therapy or the cancer early in the treatment cycle. Futility of therapy can be identified early and the availability of sufficient numbers of CTC will enable to choose only effective therapies thereby reducing healthcare expenditures and improving quality of life.

3. Impact on the research field: More effective tools to guide cancer therapy are of utmost importance. Tumor cells circulating in the blood of cancer patients can achieve this goal. However, through the state of the art of current technology only a small percentage of cancer patients can benefit of CTC based treatments. This is easily explained by the current limited ability to detect these CTC. The DLA in combination with the CTC enrichment and analysis tools developed by the CTCTrap consortium has addressed this issue. The larger number of CTC identified in the patients increases the quality of the molecular characterization of CTC and will improve the ability to choose the therapy best for the patient.

4. Innovation market: The interest for drug development and biomarker discovery further increases the promise of CTCTrap.

At present the only validated assay for CTC detection that has been cleared by the U.S. Food and Drug Administration is the CellSearch system. Janssen DXis a unit of Johnson & Johnson and markets the CellSearch in vitro diagnostic system in the U.S. to capture and count CTCs to determine the prognosis of patients with metastatic prostate, colorectal or breast cancer. With the CellSearch system CTC are detected in less than 39% of metastatic breast, colon and prostate cancer patients. The
developments within the CTCTrap program have clearly demonstrated that a larger number of CTC in more patients can be isolated. But more work will be needed to demonstrate that these additional tumor cells indeed will increase the likelihood to choose a better therapy. CTCTrap is expected to be the door opener for significant revenues in the evolving “personalized medicine” market.

List of Websites:
https://www.utwente.nl/tnw/ctctrap/

Related information

| Result In Brief | Circulating tumour cells – the gate to personalised cancer treatment |

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