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PROJECT IDEA

1. Call and Programme

- H2020 - WORK PROGRAMME 2014 – 2015
- Social Challenge 1: Health, demographic change and wellbeing
- PHC 24 – 2015: Piloting personalised medicine in health and care systems
- http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/2282-phc-24-2015.html

2. Timetable / Deadline

- Stage 1: 14 October 2014 (17:00 Brussels local time)
- Stage 2: 24 February 2015 (17:00 Brussels local time)

3. Title of the Project

PERSONALIZED THERAPY OF CANCER (PTC): Implementing an interdisciplinary cancer care model to improve results of therapy through a process of drug selection (based on genetic tumor profile), pharmacologic monitoring (based on control of systemic drug exposure) and biologic assessment of the response (based on PET imaging) in frequent solid tumour types.

4. ACRONYM

PTC

5. General description of the project (Max. 1 pg.):

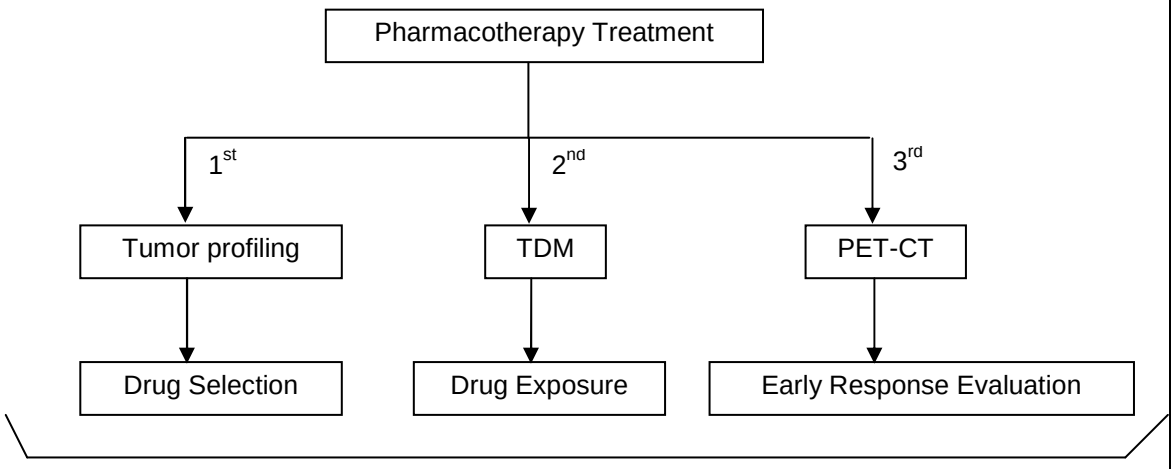
Recent advances and developments in molecular biology of cancer make possible today the evaluation of the genomic alterations of each tumor and the selection of the specific treatment in a real time basis (1, 2). However, genotype changes might not predict the clinical outcome because phenotype compensatory changes and other factors can modify the systemic drug exposure and therefore, the toxicity and/or the clinical response. These factors include polymorphisms in metabolizing enzymes and drug transporters, patient characteristics (such as gender, age, ethnicity, liver and renal function, protein levels), co-medication that can interact with the drug metabolism and disposal, co-morbidity and disease related factors (such as infection, hypertension, metastases) as well as patient adherence to treatment in case of oral anticancer therapies. This has been extensively reported in the literature (3, 4, 5).

Thus, the real tailoring cancer treatment should take in account the tumor genetic information and the drug systemic exposure that can be controlled by therapeutic drug monitoring levels (TDM). TDM is the measurement and interpretation of drug concentrations in biological fluids so as to determine the correct drug dosage for an individual patient. TDM is an important tool in personalized tumor therapy because (6):

- After selecting the correct patient and the correct drug, we often fail to confirm the correct exposure
- The majority of cancer patients have exposures outside the therapeutic window and about the 40% are underdosed
- Failure of phase III trials is due not to excess toxicity but low efficacy, partly as a result of underdosing.

Finally, the early metabolic response assessment measured by PET-FDG to predict patient outcome is the third important tool in an integrated cancer care model. Anatomic imaging alone using standard WHO and RECIST criteria has relevant limitations, particularly in assessing the activity of newer cancer therapies that stabilize disease, whereas 18F-FDG PET appears particularly valuable in such cases (6,7,8). In addition, an early performed PET could help in the identification of targeted therapy effects on pathogenic versus compensatory gene expression changes since no responses are expected in case of drugs aiming to modify compensating phenotype gene variations.

The follow diagram summarized the integrated model that actually is routinely used in the Platform of Oncology in Quirón Hospital, Torrevieja, Spain, to personalize the pharmacotherapy cancer treatment:



Personalized tumor therapy requires an interdisciplinary approach integrating decisions based in different fields of basic and clinical specialties. The translational aspects are not well developed in tertiary university cancer hospitals and monographic cancer centers, and new models of organization are deemed as necessary before establishing a fluent practice of personalized cancer treatment.

The proposed model is a virtual interdisciplinary organization that can be adapted to all hospitals since several parts (i.e. tumor profiling and pharmacokinetic studies) can be carried out extramurally in case it is needed. A virtual interdisciplinary approach is an alternative towards the desired goal of integrating health care in Europe.

The most common malignant tumors of the adult (i.e. lung, colorectal, and breast cancer) present multiple genomic alterations with therapeutic implications. Some of them are isolated changes and require simplified decisions but these occurred in a few patients. In the other hand, frequent multiple alterations are present and a patient-tumor therapeutic approach has to be defined based on patient “omics”. The difficulties in gathering and integrating all the information leads and the task of entering the patients in complex therapeutic programs, together with the elevated costs of a new technological organization appear today as an insurmountable task for the high level health care institutions.

The integrated model showed in the diagram above developed in The Platform of Oncology is a new non-departmental model of healthcare organization designed to provide and promote excellence in personalized cancer care. This open structure permits a truly interdisciplinary work characterized by the central concept of the patient, the interdisciplinary faculty organization, and the open collaboration with other health care providers. The Platform of Oncology was created in the year 2000 to develop a permanent interdisciplinary team including medical, surgical and radiation therapy oncologists, surgeons, nuclear medicine physicians, radio-physics, immunologists, pathologists, clinical pharmacologists, molecular biologists, psycho-oncologists, nurses. The most relevant fields in personalized cancer treatment are:

1. Genomic units able to study whole exome DNA and RNA expression and to identify the most frequent alterations described in selected frequent tumor types. Currently the expression of more than 150 genes related to prediction biomarkers of sensitivity and resistant to drugs, tumor pathways and new drug targets are being evaluated.
2. Quantitative Pharmacologic units to monitor drug exposure and define the optimal

exposure-efficacy-toxicity relationships for the individual patient. Nowadays, 24 HPLC methods for therapeutic drug monitoring of anticancer drugs have been developed and are used in common clinical practice.

3. Molecular imaging department, PET to monitoring the functional dynamics of tumors (*in vivo* pharmacokinetic and target identification) and to evaluate an early response.

The objective of this project is to share the integrated patient centered cancer care model in participating selected institutions and to create an European network of personalized cancer care. Several of the techniques that permit personalized cancer care can be performed on patient's biological samples (blood, serum, biopsies, etc) which can be studied extramurally. Specialized units working in a way similar to the core facilities, with the adequate coordination, can spread the benefits of personalized treatment to a wide population of cancer patients. The impact of this new model organization and the results of therapy will be measured with qualitative and quantitative indicators.

References:

1. F.S. Collins, MA Hamburg. First FDA authorization for next –generation sequencer. N Engl J Med. 2013; 369:2369-71
2. L de Mattos-Arruda, J Rodon. Pilot studies for personalized cancer medicine: Focusing on the patient for treatment selection. The Oncologist 2013:18:1180-8
3. Mathijssen RHJ, Loos WJ, Verweij J, et al. Flat-Fixed Dosing Versus Body Surface Area–Based Dosing of Anticancer Drugs in Adults: Does It Make a Difference? The Oncologist 2007, 12:913-923.
4. Saleem M, Dimeski G, Kirkpatrick CM. Target concentration intervention in oncology: where are we at? Ther Drug Monit 2012;34:257–265
5. Mathijssen RHJ, Loos WJ, Verweij J. Determining the Best Dose for the Individual Patient. J Clin Oncol. 2011;29:4345–4346
6. Beumer JH. Without therapeutic drug monitoring, there is no personalized cancer care. Clin Pharmacol Ther 2013; 93: 228–230
6. Jones T and Price P. Development and experimental medicine applications of PET in oncology: a historical perspective. The Lancet Oncology. 2012; 13 (3) 116-125.
7. Wahl R. et al. From RECIST to PERCIST: Evolving Considerations for PET Response Criteria in Solid Tumors. J Nucl Med 2009; 50:122S–150S
8. Basu S. Personalized versus evidence-based medicine with PET-based imaging. Nat Rev Clin Oncol. 2010; 7:665–668.

6. Main objectives (general and specifics):

1. To validate and demonstrate that a new model of organization in personalized cancer treatment is plausible and technically feasible and can be adopted by other institutions.

2. To use this integrated approach as a new model sharing for the personalized pharmacotherapy of cancer treatment and expanding clinical benefits and data results.

3. To develop a EU network integrating different levels of cancer care units in order to make an up-to-date offer based on personalized approach to different geographical patient populations.

4. To show the intermediate effects, benefits in health results, costs effectiveness and ethical outcomes of this Platform.

5. To accomplish a rapid translational cancer research system for the advancement of personalized cancer therapy.

7. Main actions / activities:

1. To implement and adapt the current panel of genes determined by RNA expression, related to prediction biomarkers of sensitivity and resistance to anti-cancer drugs, tumor pathways and new drug targets.

2. To develop and validate new methods of handling the biological specimens in order to extend the use of these methodologies.

3. To develop and validate methods for measuring the new oncology drugs in plasma or blood samples in order to generalize therapeutic drug monitoring.

4. To expand the numbers of patients who could have potential clinical benefit of personalized drug dosing.

5. To evaluate an early response by molecular imaging with FDG-PET, assessing the early functional and metabolic tumor changes that relate to the prediction of the response

6. To monitoring the functional dynamics of tumors (*in vivo* pharmacokinetic and target identification) by new PET tracers in oncology

7. To measure the results by:
   7.1. Feasibility results of integrating personalized therapy
      - Clinical impact analysis measuring the participation of cancer units with a customized prior approach and other institutions lacking the techniques for personalized therapy.
      - Measuring the effect on patient's quality of life after therapy (toxic/undesirable effects, simplicity of algorithms, cost of the treatment, satisfaction).
   7.2. Integrated model evaluation
      - Measuring the intervals from biopsy to therapy
      - Measuring the impact of pharmacologic monitoring on the dose adjustments
      - Evaluating the overall end-points results (PFS, OS, RR, etc) for each of the selected tumor types

8. Profile of partners

- Clinical care units with interest in entering into the field of personalized medicine in cancer
- European companies expert in innovative technologies for "omics"-applied research in translational oncology.
- Pharmacokinetic/pharmacodynamic laboratories with a high profile for routinely performing therapeutic drug monitoring of anticancer drugs.
- Groups with intermediate/high level of Pharmacometrics knowledge.
- European radiopharmaceuticals groups leader in the production, development and commercialization of PET tracers in oncology
- Molecular imaging departments expertise in monitoring early response with PET
- Molecular imaging departments' expertise in the functional dynamics of tumors (in vivo pharmacokinetic and target identification).

9. Foreseen duration and budget

- Four years
- Budget estimates from 10 – 12 Mill. Euros. Total amount will depend on the number of centers which participate in each part of the project. Partners' budget ranges from 250.000 to 1M Euros, depending on each participant site requirements**.**

10. Contact details

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