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ABSTRACT:

Predictive platforms which allow the identification of drug and / or radiation interactions which may be synergistic in causing side effects, treatment resistance and adverse effects are the goal of this deliverable. The aim is to identify biomarkers either molecular, biological or imaging markers which could be tested prospectively in clinical trials.

The validation of such biomarkers will be carried out retrospectively; in the case of molecular tests on tissue from the biobank, both cancerous and normal, and in the case of imaging tests on historical images from cohorts of appropriate patients.

KEYWORD LIST: Breast cancer, Wilm's tumour, ALL, Acute lymphocytic leukaemia, predictive biomarkers, molecular imaging, genomics, proteomics, adverse effects

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[1] **R**=Report, **P**=Prototype, **D**=Demonstrator, **O**=Other

[2] **PU**=Public, **PP**=Restricted to other programme participants (including the Commission Services), **RE**=Restricted to a group specified by the consortium (including the Commission Services), **CO**=Confidential, only for members of the consortium (including the Commission Services)

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1 Executive Summary

The recommendations and findings from this deliverable are:

1. All prognostic studies carried out retrospectively depend on biobanks which adhere to strict SOPs to collect normal and cancer tissues from patients whose follow up is uniform.
2. Prospective studies are required to validate biomarkers for response and adverse effects, and should be subject to the discipline of clinical trials
3. The ideal design of clinical trials to test biomarkers, either cellular or by imaging is the neoadjuvant form with consequent adaptive therapeutic arms, either randomised or not, so that tissue is available before and after the test intervention
4. CTCs and CECs should be considered as surrogate tissues when re-biopisies are impossible or undesirable.
5. Panels of biomarkers and imaging techniques should always be carried out, and reliance not placed on single techniques.
6. Ideally cell biomarkers should include microarrays, HTTP sequencing, RPPA/TMA protein analysis, proteomics, RNA expression profiling, SNP genotyping, and CNV/LOH determinations.
7. New imaging techniques with PET and MRI molecular markers will give insight into anatomic and functional changes associated with treatment.

2 Introduction

The purpose of this mini review is to draw up clear conditions for future study in p-medicine of predictive platforms for choice of treatment, drug and / or radiation interactions which may be synergistic in causing side effects, treatment resistance, and adverse effects. The key solution is the identification and validation of biomarkers which will be predictive. These will be molecular, biological and imaging markers, and require to be validated retrospectively, in the case of molecular tests on tissue from the biobank, both cancerous and normal, and in the case of imaging tests on historical images related to cohorts of appropriate patients, preferably taken part in either Phase 2 or randomised Phase 3 clinical trials. Biomarkers which are so validated will then be tested prospectively in clinical trial cohorts, designed as described below.

Others will work to identify biomarkers, while p-medicine will perform the validation experiments and develop algorithms.

This deliverable addresses task 13.7

3 Findings

3.1.1 Treatment Response- Biomarker Choice

The drugs used in the p-medicine trials in childrens' ALL and Wilm's tumour, and adult female breast cancer are for the most part well studied in terms of their pharmacogenomics, dynamics and kinetics. Also their patterns of side effects are well recognised, but for the most part unpredictable, even using the aforementioned properties. Predictive markers are badly needed for conventional drugs, and even more so for the new drugs which have only recently arrived on the scene which are likely to be evaluated in the lifetime of p-medicine. Arguably it should be easier to find biomarkers for these new agents, as they have been developed as targeted compounds, and marketed with a biomarker. None of the first wave of trials employs single drugs, so combinations need to be evaluated, and potential synergistic antitumour effects, as well as additive toxicities predicted. And to complicate matters radiation therapy is routinely given in the management of breast cancer, and there are proven interactions between this and chemotherapy. In some cases this can be explained at a molecular level.

Molecular biomarkers for all three tumour types are available, but only in breast cancer are they routinely used, or should be according to the latest St Gallen consensus (Goldhirsch et al, 2011). So analysis of oestrogen and progesterone receptors, ki 67 status, Her2neu functionality are now used to identify suitability of patients for drug , hormone or anti Her2 therapies, and shortly parp status will be added to that list, to give an indication of DNA repair efficiency, and tailoring of treatment with radiation and / or parp inhibitors. The absence of expression of all three of these pinpoints a special subset of patients, the so called "triple negative" group which indicates a particularly aggressive phenotype, and consequent tailored treatment is required.

Gene signatures and, less convincingly proteomic signals have been tested in a number of cancers in order to help select patients for therapy, and in adjuvant breast cancer treatment, to **spare** patients from unnecessary treatment.

Van de Viyver et al (2002) first described retrospective validation of a 70 gene signature in archived breast cancer samples from young women who had advanced enough disease (Stage 2) to require adjuvant chemotherapy. The signature separated out a group of women who did not require that therapy and could have been spared toxicity including alopecia, bone marrow suppression, skin rash, stomatitis, infertility, diarrhoea, nausea and vomiting. More significantly these patients could have been spared an increased risk in possible second malignancy. Whereas the late side effects of chemotherapy do not have a massive impact in adults, it is of huge significance in the two groups of children being studied in p-medicine. Very few predictors of late toxicity have proved useful, and this requires further study in the present project.

From the same lab in Amsterdam, Nuyten et al (2008) later described the extended use of gene signatures gained from microarrays to help predict prognosis, distant metastasis and local recurrence, therapy response to radio- and chemotherapy, and effects on normal tissue. Roukos et al, 2007 and 2010 review the field, expanding the evidence base to include a 21 gene assay (Oncotype), Her2 assays, and germline mutations for BRCA1 and 2. Parp was mentioned above and interestingly cells which are overexpressing parp display a phenotype similar to those cancer cells which have germ line mutations, and the term "BRCAness" is used to denote this phenomenon which has as yet not been explained by a suitable molecular marker. The clinical relevance is that patients whose cancers exhibit BRCAness often respond to parp-inhibitors, and to radiotherapy.

Vergan et al (2010) describe yet another gene signature which predicts response to trastuzumab response in patients with Her2 neu positive cancers, while the Amsterdam

group, Knauer et al (2010) have applied their 70 gene signature and shown that it is an independent prognostic variable in detecting patients with low risk Her2 positive cancers.

There are fewer claims for predictive signatures in doxorubicin- cyclophosphamide combinations in neo adjuvant treatment, which is a shame, as doxorubicin in particular is known to be cardiotoxic, even if, in a lesser percentage of patients than trastuzumab (see below). A novel approach by Barros Filho et al (2010) employs trios of genes and is predictive of response, but not toxicity. Viale et al (2011) uses a combination of receptor data plus ki67 to predict response (again minus discussion of toxicity) in letrozole therapy for oestrogen positive patients, and they advocate strongly against using single receptor information. Single gene information has not been revealing and will not be recommended in this project.

Single drug data are not particularly enlightening either, though class effects such as the anthracyclines may contribute to an eventual algorithm so it is of note that an important drug resistance gene MDR 1 (Ashariati, 2008) and the gene for the target molecule for the class Topoisomerase 2, (Orlando et al, 2008) are both informative in predicting activity, or lack of it (i.e. resistance) in single agent studies.

Putting data of this complexity together is no mean feat and the project will use several established techniques as baselines for comparison with new solutions emerging from this project. Examples include a human cancer-derived genomic predictor (DLDA30), a cell line-based genomic predictor [in vitro coexpression extrapolation (COXEN)], and an optimized cell line-derived (in vivo COXEN) predictor, Lee et al (2010).

New biomarkers are still being sought in leukaemia and solid tumours of children and adults. Relevant biomarkers can be identified by HTTP sequencing, RPPA/TMA protein analysis, proteomics, RNA expression profiling, SNP genotyping, and CNV/LOH determinations. Functional genetics RNAi screens assess whether particular drug combinations are particularly promising in tumours with a distinct molecular profile. It will be important to analyse signalling proteins as they may be altered in complicated ways depending on the type of tumour and whether it has already been exposed to anticancer drugs. All tyrosine kinase inhibitors tested in patients in clinical trials to date have resulted in eventual secondary resistance, even when an impressive initial therapeutic effect had been noted. Tissues require to be handled according to strictly observed Standard Operating Procedures (SOPs), particularly when conducting proteomic analyses and propagation of cancer cells in rodent systems is required. Both of these investigational assays are included in the work plan of the project.

The project also involves new ways of accessing normal and cancerous cells when re-biopsy is not feasible, eg in Wilms' tumours, including circulating endothelial cells CECs (reasonable markers of angiogenesis, see below), and circulating tumour cells (CTCs). Within the latter it is hoped that cancer stem cells will be identified in the next year or so. Their existence would be a powerful marker of drug resistance. Meanwhile CTCs offer the opportunity for identifying critical lesions which might prove to be drug targets, and pathways altered by previous drug or radiotherapy exposure, again exploitable as resistance flags.

3.1.2 Molecular imaging biomarkers

There is a clear convergence whereby molecular pathologists and molecular imaging scientists are working to quantitate and display the same cellular pathways respectively. The text above is much more voluminous than that on imaging simply due to a stagger in discovery and application of marker visualisation. But within the four years of p-medicine this will be considerably amplified. So inclusion of Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) with or without intelligent contrast agents should be employed in the p-medicine clinical trials, before and after therapeutic interventions.

Available data suggest that prognostic information can be accrued with this approach, especially when testing anti-angiogenesis treatments. There are no reliable serum markers of angiogenesis despite the plethora of scientific experimentation on the VEGF and related pathways, so for the time being MRI is the standard.

3.1.3 Adverse Effects- Biomarker Choice

The side effects of conventional cytotoxic drugs are well described, and predictive tests are not needed for many of them as the effect is uniform e.g. alopecia after anthracyclines or actinomycin. All drugs can cause idiosyncratic toxicities, but it is unlikely that they will be predictable in cancer, given the heterogeneity of the disease(s). Nevertheless it is worth trying to predict some of the problems which are due to pharmacoethnic, genomic or dynamic properties of the drugs used in the p-medicine clinical trials. When turning to the new “targeted” small molecules, and “specific” antibodies, the immediate realisation is that they are not truly targeted, and off target toxicities have now been commonplace. The mechanisms have seldom been worked out, but hopefully will be in the coming years.

A complication of predicting the adverse event profile in heavily pre-treated patients comes from the fact that previous patient exposure to different therapeutic regimens (e.g. aromatase inhibitors/chemotherapy for breast cancer) would affect the adverse event profile of each patient. The same is true when attempting patient stratification for the purpose of conducting clinical trials. In addition, CYP polymorphisms varying among patients influence drug metabolism and thus adverse event prediction.

In most of the therapeutic armamentarium short-term side effects predominate, are easily measurable and, with more work, will become predictable. As mentioned earlier, late effects especially in patients cured of their cancer can be very serious. These include cumulative drug effects such as pulmonary or cardiac toxicity with the bleomycins and anthracyclines respectively. In both cases exacerbation by local irradiation is the rule rather than the exception. Infertility in young men and women has a major impact on quality of life, and second malignancies especially leukaemias are frequently lethal. No good models exist for predicting these late effects.

For examples of local toxicity with known drugs pharmacogenetics is helpful. Patients who are heterozygous for the ALDH3A1*2 and ALDH1A1*2 allele have an increased risk of haemorrhagic cystitis and liver toxicity, respectively after high dose cyclophosphamide (Ekhart et al , 2008). Polymorphisms in the CYP family was not predictive, which is in contrast to a study in Indian women where the variant allele CYP2C19*2 was associated with lower risk of ovarian toxicity when treated with cyclophosphamide (Singh et al, 2007). Another variant, CYP2D6, is key to tamoxifen metabolism according to Schroth et al , 2010 and many others.. They recommend that MALDI-TOF MS/CNA is used for accurate CYP2D6 genotyping.

Steroid induced hypertension is a serious problem in children and adults treated for leukaemia. Prednisolone is the standard treatment in ALL and several genetic studies have shed light on the issue . Kamdem et al, 2008, studied over 600 children who had undergone successful remission induction therapy and found that 45% developed hypertension during treatment. None of the suspected risk factors (age, sex, race, white blood cell count, risk group, body mass index, or serum creatinine) were associated with hypertension. Among the polymorphisms they identified eight genes (CNTNAP2, LEPR, CRHR1, NTAN1, SLC12A3, ALPL, BGLAP, and APOB) containing variants that were associated with hypertension, while CYP3A4 and CYP3A5 showed none.

There are scattered reports of genomic approaches to predict mechanisms of action and effects of bevacizumab (Formica et al, 2011), L-asparaginase (Lorenzi et al, 2006), vincristine (Hongping et al, 2006), busulphan (Ansari et al, 2009), and irradiation (Kabacik et

al, 2011) which offer glimpses into the power of the methodology but are inconclusive. The work of Kruse et al, 2007, reminds us that study of effects of treatments such as irradiation should also be measured in normal tissues and not only cancerous samples., and as these effects may be late, and ”recalled” by subsequent treatment especially antimetabolites, careful biobanking is indicated but infrequently executed.

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