ABSTRACT BOOKLET

Karolinska Comprehenisve Cancer Day 12th of April 2024

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A National Task Force Study: Therapeutic drug monitoring of CDK4/6 inhibitors indicated for breast cancer

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Background: Monitoring breast cancer (BC) therapies, like CDK4/6 inhibitors, faces challenges due to the high variability of drug exposure. Personalized dosing through Therapeutic Drug Monitoring (TDM) benefits individual patients. Low adherence to CDK4/6 inhibitors and hormonal therapies demands new strategies, such as precise exposure measurement/dose adjustments by TDM. The need for an innovative patient-centric sampling (PCS), like the True Dose capillary kit, offers a non-invasive alternative within TDM. Dosing in oncology, relying on BSA or body weight, proves suboptimal for drugs with a narrow therapeutic window. Proper dose selection is crucial due to the steep dose-response relationship and narrow therapeutic index of anticancer drugs. Current dosing methods need to consider individual differences more. FDA's Oncology Center of Excellence (OCE) Project Optimus aims to reform the dose optimization and dose selection paradigm in oncology.

Aim: To establish a workflow for concurrently quantifying CDK4/6 inhibitors and hormonal treatments via capillary PCS. Objectives include validating the capillary kit's accuracy, assessing drug exposure variability, and determining user acceptability.

Material and Method: Eligible patients receiving CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) with hormonal treatments (aromatase inhibitors and tamoxifen) will be included from BC Departments in Sweden. Patient data, symptom measurements, and clinical information will be consistently collected. The study involves comparing intravenous (IV) blood sampling methods, assessing adherence, and validating self-testing capillary kits using LC-MS/MS methodology for exact blood concentration.

Results: With the initiation of TDM in oncology, the National Task Force Working Group marks progress in personalized medicine through TDM implementation. Tailor Dose-II (EudraCT 2017-000641-44) and TDM of TAM (NCT05133674) are ongoing trials, and several others are underway.

Conclusion: To introduce an innovative approach to TDM in BC, addressing challenges and aiming to enhance treatment efficacy and safety through personalized dosing strategies.

The Live Cell Imaging core facility: Advanced light microscopy in Campus Flemingsberg

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Real-world overall survival and characteristics of patients with ER-zero and ER-low HER2negative breast cancer treated as triple-negative breast cancer: a Swedish population-based cohort study

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ABSTRACT

Background

Estrogen receptor-low (ER-low) HER2-negative breast cancer has similar pathological and molecular characteristics as triple-negative breast cancer (TNBC), and it is questionable whether it should be considered a separate entity. When the international guidelines lowered the cutoff for ER positivity to $\geq 1\%$ in 2010, the $\geq 10\%$ threshold was kept in Sweden. ER-low breast cancer (ER 1-9%) is thus in Sweden treated as TNBC. We studied patient and tumor characteristics, treatment patterns and overall survival in a Swedish population-based cohort of patients with ER-zero and ER-low HER2-negative TNBC.

Methods

All TNBC cases diagnosed in Sweden 2008-2020 were included in a population-based cohort study. Patient, tumor, and treatment characteristics were analyzed by ER-status, and associations between subgroups compared using χ^2 test. Survival endpoint was overall survival (OS), and Kaplan-Meier curves were estimated. Cox proportional hazards models were used to estimate adjusted hazard ratios comparing ER-low to ER-zero.

Results

Of the 5655 tumors, 90% were ER-zero and 10% ER-low. ER-low tumors were grade III in 69.4% (80.8% in ER-zero, p=0.001), with a median Ki67 of 60% (63% in ER-zero, p=0.005). There were no significant differences in given chemotherapy (p=0.546). A pathological complete response (pCR) was achieved in 28.1% of ER-low tumors (25.1% in ER-zero tumors). In the unadjusted analysis of OS, women with ER-low disease had a borderline but not significantly better OS than those with ER-zero disease (HR 0.84 (95% CI 0.71-1.00), p=0.052). In the multivariable analysis, ER-status (ER-zero vs ER-low) was not significantly associated with prognosis.

Interpretation

ER-low HER2-negative breast cancer has characteristics and prognosis similar to TNBC and respond to neoadjuvant chemotherapy accordingly. Using a $\geq 10\%$ threshold for ER positivity seems reasonable based on real world outcomes. A change would provide women with ER-low tumors the same treatment opportunities as patients with TNBC, within studies and within clinical routine.

Studies on the effects of curcumin targeting CDC27 alone or combined with other inhibitors on HPV positive and negative head and neck cancer cell lines

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Background/aim. Human papillomavirus positive (HPV⁺) tonsillar and base of tongue cancer (TSCC/BOTSCC) accounting for 40% of all head neck cancer (HNSCC) in Sweden are still rising in incidence and are despite their better outcome compared to HPV-negative (HPV⁻) HNSCC (80% vs. 50% resp. 5-year survival) treated like HNSCC with chemoradiotherapy (ChRT). ChRT has severe side effects reducing the quality of life without improving the previously obtained efficacy of 80% 5-year survival with only radiotherapy (RT) given before, so new therapeutic options are urgently needed.

Previous studies by others and us have focused on identifying prognostic or targetable markers for HPV⁺ TSCC/BOTSCC. Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA) and Fibroblast Growth Factor Receptor (FGFR3) mutations have been found fairly frequently in HPV⁺ TSCC/BOTSCC and in vitro targeted therapy combining phosphoinositide 3-kinase (PI3K) and FGFR inhibitors have shown synergistic effects. More recently, upon whole exome sequencing (WES) we identified a deletion variant of CDC27 in patients with a poor prognosis.

Here we therefore wanted to investigate the effects of Curcumin a drug that potentially targets CDC27, either using it alone or combination with other inhibitors on TSCC/BOTSCC cell lines grown *in vitro* as monolayers (2D) or spheroids (3D).

Methods: The effects of Curcumin as single inhibitor or combined with other inhibitors e.g. BYL719 (a PI3K inhibitor) on TSCC/BOTSCC cell lines such as e.g. HPV⁺ CU-OP-2, and -20 and others grown as monolayers (2D) and spheroids (3D) are now being assessed. Effects of the various drug treatments will be analysed by viability (WST-1 assay), proliferation (IncuCyte S3 Live-cell Analysis System), and FACS assays on various TSCC/BOTSCC.

Results: Preliminary data using Curcumin as a single agent presented dose dependent responses with decreased viability and proliferation. Combination experiments are now ongoing.

Conclusion: To summarize, our preliminary data disclose that using Curcumin as a single agent reveals promising effects on HPV⁺/HPV⁻ TSCC/BOTSCC cell lines.

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Antibody-displaying extracellular vesicles for targeted cancer therapy

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Introduction

Extracellular vesicles (EVs) function as natural delivery vectors and mediators of biological signals across tissues. EVs can be engineered to display targeting and therapeutic moieties and can shuttle cargo over biological barriers. EVs can thus act as natural vectors and offer a unique platform for a new class of therapeutics. Here, we introduce the use of antibody(mAb) decorated therapeutic EVs (Fc-EVs).

Methods

Following optimization by a systematic comparison of different Fc-binding and EV-sorting domains, the broad potential of this platform is shown by mAb guided targeting in vitro and in vivo with focus on targeted cancer therapy.

Results

We show that this approach renders highly efficient targeting of EVs to HER2+ breast cancer cells and to malignant melanoma cells by the display of HER2- and PDL1-mAb, respectively. As proof of concept, Fc-EVs were loaded with doxorubicin and decorated with the immune checkpoint inhibitor PD-L1-Ab to treat malignant melanoma in vivo. The targeting approach with tumour-specific mAb allows for a dual therapeutic role as it 1) directs the doxorubicin loaded EVs to the tumour and 2) the PD-L1-Ab itself function as a therapeutic intervention by blocking the immunosuppressive PD1/PD-L1 axis. In fact, Fc-EVs displaying PDL1-Ab significantly accumulated in tumour tissue and, when loaded with doxorubicin, resulted in a

significant lower tumour burden, and pronounced increased survival of tumour bearing mice following systemic treatment.

Summary/Conclusion:

Here, we take advantage of the ability of EVs as a delivery vector and decorate them with mAb by equipping the EVs with an mAb binding moiety. We here show efficient tumour targeting and treatment in vitro and in vivo. These Fc-EVs can be decorated with different mAb and can thus be targeted to virtually any tissue of interest and could be adapted to display other moieties, including Fc-fused proteins, bi-specific mAb and mAb–drug conjugates.

Implementing data on targeted therapy from the INFORM registry platform for children with relapsed cancer in Sweden

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Background: Advances in treatment of childhood malignancies have improved overall cure rates to 80%. Nevertheless, cancer is still the most common cause of childhood mortality in Sweden. The prognosis is particularly poor for relapse of high-risk malignancies. In the international INFORM registry, tumor tissue from patients with relapsed, refractory, or progressive pediatric cancer as well as from very-high risk primary tumors is biologically characterized using next-generation sequencing to identify possible therapeutic targets. We analyzed data from Swedish children included in the INFORM registry concerning patient characteristics, survival, sequencing results and whether targeted treatment was administered to the children based on the molecular findings.

Methods: A registry-based descriptive analysis of 184 patients included in the INFORM registry in Sweden during 2016-2021.

Results: The most common diagnoses were soft tissue and bone sarcomas followed by high grade gliomas [including diffuse intrinsic pontine glioma (DIPG)]. Complete molecular analysis was successful for 203/212 samples originating from 184 patients. In 88% of the samples, at least one actionable target was identified. Highly prioritized targets, according to a preset scale, were identified in 48 (24%) samples from 40 patients and 24 of these patients received matched targeted treatment but only six children within a clinical trial. No statistically significant benefit in terms of overall survival or progression free survival was observed between children treated with matched targeted treatment compared to all others.

Conclusion: This international collaborative study demonstrate feasibility regarding sequencing of pediatric high-risk tumors providing molecular data regarding potential actionable targets to clinicians. For a few individuals the INFORM analysis was of utmost importance and should be regarded as a new standard of care with the potential to guide targeted therapy.

The CRISPR Functional Genomics Unit

Stefina Milanova, Ph.D. CRISPR Functional Genomics CFG

The CRISPR Functional Genomics (CFG) unit supports high-throughput CRISPR/Cas applications. CRISPR/Cas allows targeted gene knockout, editing, or transcriptional modulation. One powerful application is pooled screening, where thousands of genes can be targeted in parallel in a population of cells. This population is then enriched for a phenotype of interest, typically by growth advantage, drug selection, or cell sorting. Finally, enriched and depleted CRISPR guides are determined by NGS to identify novel genes involved in the phenotype of interest.

CFG performs pooled CRISPR screening from screen design to data analysis. In addition to CRISPR knockout screening, CFG offers CRISPR-i(nhibition) and a(ctivation), in which nucleasedead dCas9 is fused to transcriptional effectors and targeted to elements of interest. We also have a workflow where CRISPR/-Cas screening is coupled to single cell transcriptomics (CRISPR-scRNASeq, PERTURB-Seq, CROPSeq) and are developing in situ guide sequencing directly on microsopy slides to correlate perturbations with complex phenotypes.

Finally, we are applying CRISPR/Cas targeted base-editing for saturating mutagenesis of elements of interest, which is of interest in drug-target and protein-protein interaction studies.

Targeted deep sequencing of circulating cell-free tumor DNA for comprehensive genomic profiling in Hodgkin lymphoma

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Objective:

Genetic profiling of classical Hodgkin lymphoma (cHL) to refine diagnosis is challenging owing to the rarity of malignant Hodgkin-Reed-Sternberg cells in tissue biopsies. Analyzing plasma circulating cell-free tumor DNA (ctDNA) has emerged as a promising, minimally invasive approach for characterizing somatic aberrations at diagnosis and for monitoring of treatment response. In this study, we aim to evaluate the clinical feasibility of analyzing ctDNA in cHL.

Methods:

We included 36 cHL patients at Karolinska University Hospital, treated with ABVD/AVD±radiotherapy or escalated BEACOPP. Plasma samples were collected before, during and after treatment. Comprehensive genomic profiling of cHL, including characterization of single nucleotide variants (SNV), short insertions/deletions (indels) and copy-number variants (CNVs), was performed using the GMS Lymphoid panel to sequence ctDNA from plasma and matched genomic DNA. The GMS Lymphoid panel spans full coding sequences of 258 genes implicated in lymphoid malignancies. Libraries containing unique molecular identifiers (UMI) to enable error-correction and identification of variants with low variant allele frequency (VAF), were sequenced at a depth of 100 million read pairs using the NovaSeq 6000 instrument. Bioinformatic analyses and somatic variant calling were performed using the BALSAMIC-UMI pipeline.

Results:

Non-synonymous, protein coding somatic SNV/Indels were identified in all 36 patients, with a median of 19.5 variants/patient (range 3-68). Variants with VAF \geq 0.63% were detected in known genes implicated in HL including *SOCS1*, *TNFAIP3*, *GNA13*, *B2M*, *ARID5B*, and *STAT6*. Onwards, we will perform comprehensive genomic analysis, including CNV profiling of the entire cohort. We will also assess the prognostic value of ctDNA analyses by correlating with clinical markers and PET evaluations during and after treatment.

Conclusion:

We have preliminarily shown the potential and feasibility of targeted deep sequencing of ctDNA using the GMS Lymphoid panel for genomic profiling in cHL to improve and refine cHL diagnostics and disease monitoring during follow-up.

<u>Poster 9</u> KI Biobank – Research Core Facility at KI Li-Sophie Rathje, PhD

KI Biobank at Karolinska Institutet in Solna is a modern and high-tech infrastructure for preanalytical handling, storage and distribution of human biological samples. We provide services for collection, handling, storage and traceability of biobank samples and support scientists both within and outside of Karolinska Institutet. KI Biobank assists researchers with advice on how to start a sample collection, how the specimen should be collected and labeled, and what legal requirements that must be met in order to be able to collect human biological samples. The new Swedish Biobank Act (2023:38), valid from the first of July 2023, represents a modernization of the previous law. We help to establish the necessary agreements under the Biobank Act, such as biobank agreements, extradition treaty and Material Transfer Agreement (MTA). We offer design of study specific paper referrals and automated sample handling, such as for example plasma- and serum aliquoting, DNA extraction, preparation of cell-free plasma DNA (circulating cfDNA) from STRECK tubes, formatting of samples before analysis, and assistance with various forms of transportation. We also provide robust IT systems, ensuring full traceability of each sample for customers with samples stored at the KI Biobank as well as other departments at KI.

Pharmacological activation of p53 reduces blood vessel growth by inhibiting endothelial cell proliferation

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3) DeliverTides LLC

Therapies that inhibit tumor blood vessels from using the vascular endothelial growth factor (VEGF) to grow are a key part of treating certain cancers. However, since tumors can acquire resistance to available anti-VEGF therapies, alternative therapies that inhibit blood vessel growth through different mechanisms are needed to counter this resistance. Reduced vessel growth has been observed in tumors treated with pharmacological activators of p53, such as those that inhibit the p53-MDM2/MDMX interaction. Yet, the molecular and structural mechanisms of how p53 activation inhibit vessel growth remain largely unknown. Here, using pharmacological activators of p53, we show that activation of p53 reduces vessel growth in vitro and in vivo. On a molecular level, these activators induced cell cycle arrest at nanomolar concentrations and apoptosis at micromolar concentrations. These effects were associated with global changes in proteins involved in DNA replication, cell cycle, and stress response. On a structural level, activation of p53 reduced the connectivity between endothelial cells of the growing vessel but did not measurably affect endothelial cell migration. Together, our results indicate that pharmacological activation of p53 in endothelial cells reduces vessel growth primarily by inhibiting their ability to proliferate, affecting a specific phenotype of endothelial cells that is needed to form the growing vessel. These findings suggest that p53 activators could be an alternative type of therapy to inhibit blood vessel growth.

Poster 11 The PCM program at Karolinska Institute

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Precision Cancer Medicine (PCM) emerged during the recent 15 years as a result of the biomedical revolution in understanding cancer biology and technical developments of novel powerful molecular tools .

The PCM program at KI was initiated ten years ago as a platform to support research on PCM and its implementation in translational cancer research with close-to-patient applications.

The program vision is that PCM shall be adopted as a leading treatment concept in academic cancer healthcare in Stockholm, aiming for real-world achievements with a sustainable and stress tested organization. This is now in progress thanks to the establishment of Precision Medicine Center Karolinska (PMCK) since three years. PMCK will be a major end-user of the results from PCM-research.

For PCM to succeed it is fundamental to achieve a sustainable working mode, a shift in working procedures and attitudes. PCM depends on many stake holders and competencies which typically act in silos in a fragmented way and need to come together in team science collaborative modes.

The program has supported and catalyzed central issues for elevating PCM to the clinical level: implementation of molecular diagnosis based on genomics, a user friendly clinical decision tool, liquid biopsy screening, and PCM beyond genomics: symptomics, broader phenotyping, and in vitro drug testing.

We consider the enrollment of more patients into early clinical trials together with international collaboration and benchmarking to be engines for future success of precision health and medicine.

We catalyzed the new early clinical trials with novel design adapted to PCM with our international partners through Cancer Core Europé (CCE), Basket of Basket (BoB).

The PCM program underwent an international scientific evaluation in 2021 which supported our approach and suggested that Stockholm could be internationally competitive in this field. The PCM program is currently being funded by Radiumhemmets Forskningsfonder until spring 2025.

Pathology is the study of diseases at the levels of organs, tissues, cells and molecules Division of Pathology, Department of Laboratory Medicine, KI

Pathology integrates subjects such as anatomy, histology, physiology, immunology, and celland molecular biology to understand causes and mechanisms for development and progression of various disease conditions. In our division, we conduct cross-boundary research in its character, and uses established and modern methods in approaching problems in the areas of cancer, inflammatory and immunological conditions as well as certain degenerative diseases. Research in pathology is closely linked to the clinical diagnostic services in clinical pathology and cytology, which are part of laboratory medicine. The clinical samples are extensively used for research purposes, and an increasing number of samples are stored in biobanks for future analyses. Teaching in pathology is provided at the basic and advanced undergraduate levels, doctoral education, and occupies a central position in education to physicians and dentists. Pathology is also taught for students in biomedicine, nursing, and biomedical laboratory science. Besides being an important subject in research education for graduate students, competence in pathology is often requested in clinical research studies, making academic and clinical pathologists a suitable collaborative partner. Welcome to our poster and discuss study, research, and employment opportunities.