

Preclinical validation of Notch therapeutics for cancer treatment

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Valorization addendum

Clinical relevance

Cancer is one of the major causes of mortality worldwide. Despite significant advances in the understanding, prevention, and treatment of cancer, the disease continues to affect millions of people worldwide. Cancer patients primarily undergo surgery, radiotherapy, chemotherapy or any combination of these treatment strategies to prolong life, but ultimately the disease relapse due to the treatment failure. For GBM multiforme (GBM), only about 3.4% of patients survive more than 5 years. For lung cancer patients, the five-year survival rate is about 50% and 4% at early and late stages of the disease, respectively. Therefore, there is a great need for better treatment approaches to further improve the clinical outcome.

Increasing evidence suggests that the NOTCH signaling is frequently deregulated in many solid cancers. GBM and Lung cancer, which have been studied in this thesis are examples of cancers that have been shown to benefit from NOTCH pathway modulation. This has stemmed from the fact that different NOTCH pathway components display altered expression in these cancers and that NOTCH signaling impact on properties associated with tumor initiation and progression in these cancers. Consequently, NOTCH modulating drugs are now entering the early phase clinical trials.

In this thesis, we demonstrated the involvement of NOTCH activity in poor prognosis and radiation resistance of non-small cell lung cancer (NSCLC) suggesting that blocking NOTCH activity in tumors may improve NSCLC outcome after radiotherapy. We also obtained promising results on the increased efficacy of the standard care of treatment (radiation and chemotherapy) when is combined with a clinically relevant NOTCH inhibitor (RO4929097) in an orthotopic GBM model. Currently, in a phase I clinical trial the efficacy of the RO4929097 NOTCH inhibitor in combination with standard radiation and chemotherapy (temozolomide) is being evaluated for GBM. Although NOTCH modulating drugs are now entering the early phase clinical trials, the use of these drugs to achieve positive clinical outcome has been limited due to dose-limiting toxicity and lack of efficacy. Use of these drugs can only be successful if these hurdles can be overcome. For example, an appropriate treatment scheduling could make NOTCH targeted therapies a safe treatment strategy. Additionally, Identification and validation of NOTCH molecular signatures as a surrogate for pathway activation and inhibition could be used to allow selection of a subset of patients who are likely to benefit from the Notch targeted therapies.

The work presented in this thesis demonstrates a potential for the use of Notch inhibitors in combination with radiotherapy and chemotherapy in models for brain and lung cancer. Effective translation to human studies is best achieved when preclinical models closely follow clinical treatment practice Thus, like in clinical

oncology practice, preclinical models developed here are adapted with non-invasive imaging modalities to follow drug distribution and uptake, tumor growth kinetics and response as well as treatment planning for precise radiotherapy. At present, radiation in most preclinical models is given using broad beam X-ray techniques, making use of lead shielding to focus the radiation on a precise area. At Maastricht clinic, we have access to a state-of-the-art image-guided precision small animal irradiator nicknamed *SmART* (Small Animal RadioTherapy) that combines micro-CT imaging with conformal irradiation beams as small as 1-mm in diameter. This means that researchers can target irradiation to an exact anatomical target and deliver much higher doses while limiting normal tissue exposure and potential toxicity. Using advanced techniques and devices in NOTCH preclinical research allows us to confidently assess preclinical treatment regimens closely following patient routine treatment.

Societal relevance

The prevalence of cancer and its mortality rate is not only affecting human health but also greatly influencing economical stability in the world. Drug development for cancer treatment is one of the major costs of cancer in society. Millions of dollars are spent in preclinical research to identify a compound or design a drug, describe its mechanism of action and generate preclinical data. It also costs us the people we love.

The scientific findings of this thesis suggest a potential for the use of Notch inhibitors in conjunction with standard of care treatment, which would result into benefitting patients. More studies are needed to substantiate our findings but they encourage the initiation of patient studies. Differences in NOTCH expression status of the patient's tumor provide information on their varied response to NOTCH inhibitors. In this regard, identification of a NOTCH biomarker to provide information on the NOTCH activity status and predict its response would be extremely important in the context of personalized medicine. This could allow identification of a subset of patients who are likely to benefit from the targeted therapies. Furthermore, appropriate scheduling for NOTCH inhibitors in conjunction with other treatments would improve therapy outcome. Together, these findings may result into more effective therapeutic ratio when using Notch inhibitors in patients.

Products

The result of the presented research could be introduced into clinic by producing antibodies, peptides or small molecule inhibitors that could be able to target

NOTCH signaling at different stages in the pathway. Current NOTCH-targeted therapies are mostly pan-NOTCH inhibitors and are burdened by side effects in normal tissues that limit their applicability. Several potential ways to overcome the observed and dose-limiting side effects have already been considered. For example, co-administration of glucocorticoids could greatly ameliorate the adverse effect while maintaining the anti-tumor efficacy. The clinically relevant RO4929097 NOTCH inhibitor used in this research is a pan-NOTCH inhibitor and by using an intermittent dosing schedule, we and others observed no dose-limiting toxicities

Innovation

The concept of combining NOTCH inhibitors with standard care of treatment in cancer is not new and several clinical studies are ongoing. However, the study described in chapter 7 is the first to show that NOTCH inhibition increases the efficiency of the standard care of treatment (radiotherapy and temozolomide) in GBM patients. Additionally, implementation of an advanced image-guided radiotherapy for scaling down radiation technology for use in small animals and application of a treatment planning software (*SmART* plan) to precisely perform the radiation treatment is a novel technology in the field of preclinical animal research. Currently, the majority of animal data acquired from radiation research in glioblastoma models are derived from imprecise irradiations that have almost no resemblance to modern clinical radiotherapy. Here, we show that dedicated micro-irradiation devices that deliver conformal accurate dose to localized regions using image guidance greatly improve current preclinical research and will improve the translation of novel combination therapies into the clinic. We expect that the results from these studies have a higher chance of yielding success in human studies than traditional models.

Market opportunities

While the finding of this thesis does have a potential clinical relevance with a gain for society and could eventually lead to an improved outcome for treatment of the cancer patients, its direct translation from bench to bedside for daily clinical practice needs further investigation. Current preclinical work including the data shown in this thesis indicates that NOTCH pathway inhibitors are unlikely to be effective alone, but that they can significantly increase the efficacy of current therapies. Consequently, several clinical trials for different types of cancers are underway to test how well NOTCH inhibitors are tolerated when combined with chemotherapy or radiotherapy, and whether any added benefit is observed. For example, clinical trials have reported that the RO492907 NOTCH inhibitor combined with chemotherapy resulted in stable disease in some pancreatic,

tracheal and cervical cancer patients. There is also a phase I clinical trial for the combination of RO492907 NOTCH inhibitor with current standard care of treatment for GBM patients. If these results and the following trials (II and III) are promising, the drug still needs to be authorized for marketing. These regulations are carried out by regulatory agencies such as FDA or WHO. In total, the process may take up to 10 years before the new treatment can be used in daily clinical practice.

All said, there are some difficulties with applying the new drug combination strategy. For example, there is a need to identify patients that are likely to respond to NOTCH pathway inhibitors. In addition, one major caveat that emerged from the initial preclinical studies and phase I trials of NOTCH-inhibiting drugs is a dose-limiting toxicity gastrointestinal toxicity. A potential solution to ameliorate the gut toxicity is through intermittent dosing schedules and corticosteroid administration. Additionally, there are other potential risks of using NOTCH inhibitors due to extensive crosstalk of the NOTCH pathway with major pathways during development. Despite this, NOTCH inhibitors generally seem well-tolerated. More studies are needed to validate the additive value of NOTCH inhibitors in combination therapies before they may be introduced to the health care market. At present, given the large number of disease settings in which aberrant NOTCH signaling is involved, there is a pressing need to develop safe and efficient NOTCH-based therapies. Despite difficulties in successfully bringing NOTCH inhibition to the clinic, there is growing optimism that NOTCH inhibition will become an exciting new addition to cancer treatment armamentarium.

While the pharmaceutical industry is challenged by the development of novel compounds and the proof of clinical evidence of marketed compounds in novel chemo-radiotherapeutic settings, this market analysis did not reveal any unmet need related to animal radiation. Precise animal radiation provides opportunities to test the effect of radiation in conjunction with novel or existing oncology compounds *in-vivo* with high potency to translate towards clinical application. In particular, the field of chemoradiation is considered highly attractive, as a developing field, which opens opportunities for both novel as well as well-established cytotoxic compounds to be tested *in vivo*. In this regard, there is a great market need for small animal irradiators and the treatment planning software (*SmART* plan).

In conclusion, our promising result on enhanced treatment efficiency using NOTCH inhibitors in combination with radiation and chemotherapy using an advanced image-guided radiotherapy and the newly commercially available treatment planning software introduce a new treatment strategy for enhancing therapy outcome in GBM patients and possibly other cancer types. Our results provide

proof of principle for the implementation of this approach in other preclinical settings for cancer treatment as well.