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Mini Review
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Tarpgaard et al is: Repurposing of Drugs in Chemotherapy Resistant Colorectal Cancer

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Abstract

Chemotherapy resistance remains a major clinical problem in the current treatment of cancer patients and chemotherapy resistance almost inevitably occursin metastatic cancer patients.In colorectal cancer patients, the response rates to first line chemotherapy therapy is approximately 50%, dropping to approximately 10-20% in second line treatment and no standard third line treatment exists. Thus, there is an obvious and acute need for novel drugs to increase response rates. Here, we focus on the promising idea of repurposing existing drugs in clinical trials with chemotherapy resistant colorectal cancer patients and suggest a general clinical trial design that could be employed to test repurposed drugs.

Introduction

Drug resistance,being de novo or acquired, represents a major clinical challenge in today's treatment of cancer patientsresulting in a large fraction of patients receiving chemotherapy without any beneficial effects while they almost all experience drug related site effects [1]. Overall, it has been estimated that the response rates of cancer patients to chemotherapy are as low as 25% [2]. One way to tackle this problem is to develop and use predictive biomarkers, which can be used to allocate the right treatment to the right patient at the right time. Predictive biomarkers can be markers for drug sensitivity or markers for drug resistance [3]. Predictive biomarkers appear to have most impact in early line treatment since many patients will develop cross resistance and thereby multi drug resistance over the course of different treatment lines. In fact, drug resistance may cause treatment failure in over 90% of patients with metastatic cancer [4]. This short commentary will focus on the use of repurposing drugs to overcome drug resistance in colorectal cancer (CRC) patients as drug resistance is considered the single most important obstacle to greater success with chemotherapy for patients suffering with this disease [5].

CRC still represents a major health problem being the third most frequent cancer form in males and second most frequent in females with 1.4 million new cases and 700,000 deaths from CRC in 2012 in the Western World [6]. These numbers clearly illustrate that treatment of CRC is still far from optimal and despite the recent introduction of a number of new treatment options for this disease, a large number of patients continue to die from CRC.

Surgery is still the only effective treatment of CRC. However, the success of the surgical treatment entirely depends on the stage of disease being presented at time of surgery. Patients with high risk stage II or stage III CRC are offered adjuvant treatment in order to reduce the risk of disease recurrence after surgical removal of all visible lesions. Adjuvant medical treatment of CRC has not changed significantly for a decade and approximately 25% of the treated stage II patients and 40% stage III patients will experience disease recurrence despite systemic adjuvant treatment [7]. In patients with metastatic CRC (mCRC) today's treatment includes conventional chemotherapy based on only three cytotoxic drugs: fluorouracil (5-FU), oxaliplatin and irinotecan. These drugs are used in combinations of 5-FU/capecitabine/S1 plus leucovorinin combination with either oxaliplatin or irinotecan, and in some cases in combination with targeted biological treatment (EGF-receptor blockade or anti-angiogenic treatment) [8-10]. The response rate to first line treatment of mCRC is approximately 50% independent on which of the above mentioned drug combinations that are used but unfortunately, most of these patients will develop drug resistant disease as evidenced by progression of their cancer [11]. Objective response rates to second line treatment are reduced to 10-20% depending on the drug combination used [11]. However, all of these patients will

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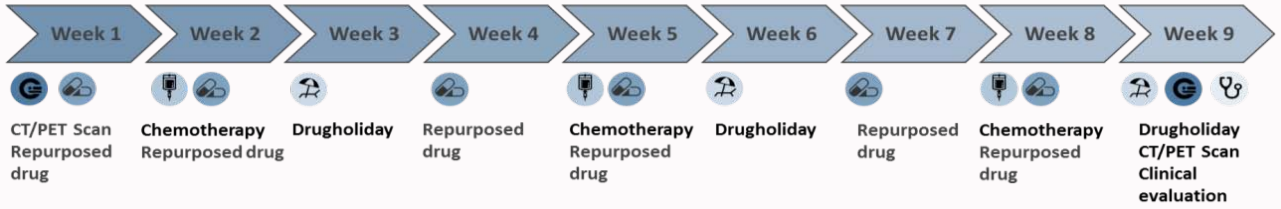

Figure 1: Design for clinical Phase II studies with repurposed drugs in combination with chemotherapy in cancer patients that have become resistant to the chemotherapy.

experience disease recurrence/progression. There is no standard third line therapy, but the third line treatment chosen by the oncologist can induce a short increase in progression-free survival and overall survival but without meaningful tumor regression.

From the above mentioned it is evident that drug resistance in CRC represents one of the most important clinical challenges in today's treatment of CRC patients. This problem can be alleviated in several ways, including improved early diagnosis (down-staging), reliable predictive biomarkers, novel drugs/drug combinations, repurposing of existing drugs, and optimized administration schedules.

We have chosen to focus on the very promising possibility to repurpose/reposition existing drugs. Repurposing of drugs is an alternative to the classical pipeline of drug development and there has been increasing interest in analyzing anti-cancer activity of non-cancer drugs already in the existing FDA approved drug armamentarium [12]. Overall, the repurposing strategy possesses two major advantages. Firstly, prior knowledge of e.g. pharmacokinetics, toxicities and dosing can be utilized in the drug repurposing. Secondly, many of the candidates for anti-cancer drug repurposing are at very low cost in contrast to the very expensive novel agents.

Obviously, the candidate drugs for repurposing in CRC need to be tested in a suitable clinical set-up. Currently, we are conducting a "windows of opportunity" Phase II clinical trial in Denmark in which we repurpose an anti-cancer agent (epirubicin) in mCRC [13]. This is a biomarker (Topoisomerase IIa gene copy number) guided trial based on Simon's two stages Mini-max design, which ensures early study termination if there is insufficient effect [14].

When repurposing a drug, which is not currently used as anti-cancer agent, there is a potential risk that the drug in combination with the standard chemotherapy hasunexpected toxic effects. Thus, we suggest a "three + three dose escalating" clinical trial design in which a run-in study is conducted to minimize the risk of adverse toxic events 8 (Figure 1). The concept is that patients are included in cohorts of three at progressively higher dose levels of the repurposed drug. All patients will receive standard concentrations of chemotherapy in combination with the repurposed drug. Initially, three eligible patients are included with standard chemotherapy in combination with the repurposed drug in a dose that is 50% of the previously established maximum tolerated dose (MTD). If dose limiting toxicity (DLT) is observed in one of three patients during the first course of treatment, three additional patients will be added at the respective dose level. Dose escalation will continue only if none of three or one of six patients experience DLT. In this case, dose escalation will continue to 75%of the MTD and the same procedure will be followed. At the highest dose of the repurposed drug six patients will be included. These six patients will also be included in the following Phase II study to minimize the number of patients in the trial. The phase II study will follow the Simon's two stages Mini-max design [14].

We are currently planning such a repurposing study with disulfiram (Antabuse) in patients with mCRC who failed first line systemic treatment. In preclinical models (isogenic pairs of parental chemotherapy sensitive and chemotherapy resistant cell lines) we have observed that disulfiram in combination with copper significantly increases the anti-tumor effects of irinotecan in oxaliplatin resistant CRC cells or increases the effects of oxaliplatin in irinotecan resistant mCRC cells [15]. The study will also be a "window of opportunity" study with a run-in study preceding the main phase II study as described above. We consider this design to be a general design for clinical trials of repurposed drugs when given in combination with standard chemotherapy in patients with metastatic cancer.

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