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Diagnostic validation and interpretation of longitudinal circulating biomarkers using a biomarker response characteristic plot

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ABSTRACT

Background: Serum-based tumor biomarkers are used to monitor cancer treatment, while clear guidance on the clinical usage is often lacking. We describe a graphical presentation to support diagnostic accuracy studies and clinical interpretation of longitudinal biomarker data.

Methods: A biomarker response characteristic (BReC) plot was designed. To allow demonstration of the BReC plot application, software was developed that supported 1) dynamic generation of BReC plots, and 2) diagnostic accuracy studies of biomarker response-based medical tests. The BReC plot application was demonstrated using serial carcinoembryonic antigen (CEA) and Cyfra 21.1 results from 216 patients with metastasized non-small cell lung cancer, treated with Nivolumab in routine clinical practice.

Results: The developed software supported the generation of BReC plots and diagnostic validation of biomarker response-based medical tests by generating the sensitivity, specificity and predictive values. Obtained BReC plots showed a clear relationship between clinical outcome and CEA and Cyfra 21.1 responses. Furthermore, using BReC plots, CEA and Cyfra 21.1 based medical tests were designed with a sensitivity for detection of treatment failure of 0.34 and 0.35 and a specificity of 0.96.

Conclusions: The BReC plot appears to support diagnostic validation studies and the interpretation of longitudinal biomarkers though further validation is warranted.

1. Introduction

In medical oncology, serial analysis of tumor biomarkers is used to provide an early indication of changes in tumor burden [1]. Although several serum-based tumor biomarkers are available and used in clinical practice for follow-up purposes [2–4], clinical interpretation of individual patient results remains challenging. The observed tumor biomarker dynamics depends on various variables, including: i) biomarker half-life, ii) therapeutic intervention, iii) analytical variation of the assay, iv) pre-analytical variations, v) biological variations [5], vi) other not-tumor-related processes such as renal or liver failure [6], and vii) tumor dynamics and heterogeneity. To estimate the relevance of two successive biomarker results the reference change value, based on analytical variation and biological variation determined in healthy controls, is often recommended [1,5]; however, it is uncertain whether this value reflects all previously established variables relevant for the interpretation of consecutive tumor biomarkers. As a result clear guidance regarding the clinical meaning of consecutive tumor biomarker results is lacking for many tumor biomarkers available and used in clinical practice.

Longitudinal circulating tumor biomarkers are most often used for the follow-up of cancer treatment in order to “diagnose” response or absence of response to (systemic) treatment or “diagnose” recurrent disease after (curative) treatment. There are several challenges related to the process of diagnostic validation of longitudinal biomarkers. The first is what kind of metric to use to describe the ‘pattern’ of consecutive

Abbreviations: BReC plot, biomarker response characteristic plot; CEA, carcinoembryonic antigen; Cyfra 21.1, cytokeratin 19 fragment; RECIST, response evaluation criteria in solid tumors; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; CPD, Clinical progressive disease; IT, information technology; SQL, structured query language; HTML, hypertext markup language; NPV, negative predictive value; PPV, positive predictive value

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biomarker results and what method to use to describe results obtained over time. Approaches used to describe and validate the longitudinal biomarker response include (or are based on): logical and criteria-based rules [7,8], doubling time [9], kinetics [10], population pharmacodynamics modeling [11], random-effect models [12], and latent class growth curve modeling [12]. A second challenge is to select relevant time points for the biomarker results and the clinical reference standard. Since time intervals at which biochemical, radiological or clinical responses occur may differ [13,14], improper selection of the clinical reference time point (e.g. at the same time as the biomarker sampling) might conceal the true diagnostic properties of a biomarker. Also, methodological characteristics (e.g. study design, patient selection and populations, quality of clinical reference standards) can affect the quality of diagnostic accuracy studies [15]. All these issues complicate the diagnostic validation of longitudinal biomarkers.

To support the diagnostic validation and clinical interpretation of longitudinal (tumor) biomarkers, we present a graphical tool that relates biomarker responses to clinical reference standards later in time, i.e. the biomarker response characteristic (BReC) plot. This descriptive graphical presentation is suggested to support biomarker response based medical test design, modeling of longitudinal data and the clinical interpretation of biomarker responses. In order to be able to demonstrate its potential use, software was developed that supported the dynamic and flexible generation of BReC plots and diagnostic validation of biomarker response based medical tests. Furthermore, metastatic non-small cell lung cancer patients treated with Nivolumab immune checkpoint therapy in routine clinical practice and regularly monitored using carcinoembryonic antigen (CEA) and Cyfra 21.1, was used as illustrative patient cohort. Studies to investigate these tumor biomarkers as early response assessment tools for these patients are subject of future research.

2. Material and methods

2.1. Patient and laboratory data

The BReC plot application was demonstrated using tumor biomarker data obtained from 216 patients with metastatic non-small cell lung cancer treated with Nivolumab in routine practice [16]. These patients were monitored every other week for a panel of tumor biomarkers, including CEA and Cyfra 21.1, measured on a Roche cobas 6000 system. Furthermore, clinical status was scored every 3 months after start of therapy that could result in the following responses, i.e. based on radiological observations (response evaluation criteria in solid tumors; RECIST 1.1): i) complete remission (CR), ii) partial remission (PR), iii) stable disease (SD), and iv) progressive disease (PD) [17]; furthermore, v) death (deceased), and vi) treatment discontinuation due to clinical progressive disease (CPD) were scored. All tumor biomarkers were analyzed prospectively in a routine care setting [16].

2.2. Biomarker response characteristic (BReC) plot generation

BreC plots were generated for individual biomarkers. The longitudinal biomarker data were analyzed by defining two biomarker time points i) a baseline time point and ii) a follow-up time point. Both these time points are related to the starting time point of the intervention (start of Nivolumab treatment) that is designated as 0. Both the time point of the baseline measurement and follow-up time point are reflected by an editable time interval expressed as time from (or to) start of the treatment and both are chosen by the user. In the present setup, these are expressed in week units. Every patient is included for whom a numerical result of the specified biomarker is available within the selected baseline and follow-up time intervals. When more than one tumor biomarker result was available within a baseline or follow-up time interval then, for the baseline tumor biomarker result, the result closest to the start of the intervention was selected, whereas for the follow-up time the latest tumor biomarker result after the intervention was selected. Next, the follow-up result is expressed as a percentage (%) change relative to the baseline result (biomarker response). For every patient included, (i.e. with a valid biomarker response) the clinical response (e.g. deceased, CPD, PD, SD, PR, or CR) observed at 3 months, 6 months, 9 months, etc. was selected. Next, the biomarker response observed at the follow-up time point was plotted on the x-axis and (per biomarker response interval) all observed clinical responses of interest were plotted proportionally and are color-coded in a bar. This graph is called a 'biomarker response characteristic (BReC) plot'. A biomarker threshold was optional to allow excluding patients from the BReC plot when both biomarker results (i.e. at baseline and follow-up) were below the set threshold.

2.3. Information technology setup

An information technology (IT) infrastructure was developed for data management and to support a dynamic interface that can automatically generate BReC plots. Microsoft SQL Server 2016 database software was used to make use of R programming language directly on the database. The database contained tables with all available biomarker concentrations and the clinical response information from all monitored patients. These data were sorted into a timeline for each biomarker of each patient and linked to the clinical response. This was done using multiple stored procedures containing the code of a combination of structured query language (SQL) and the programming

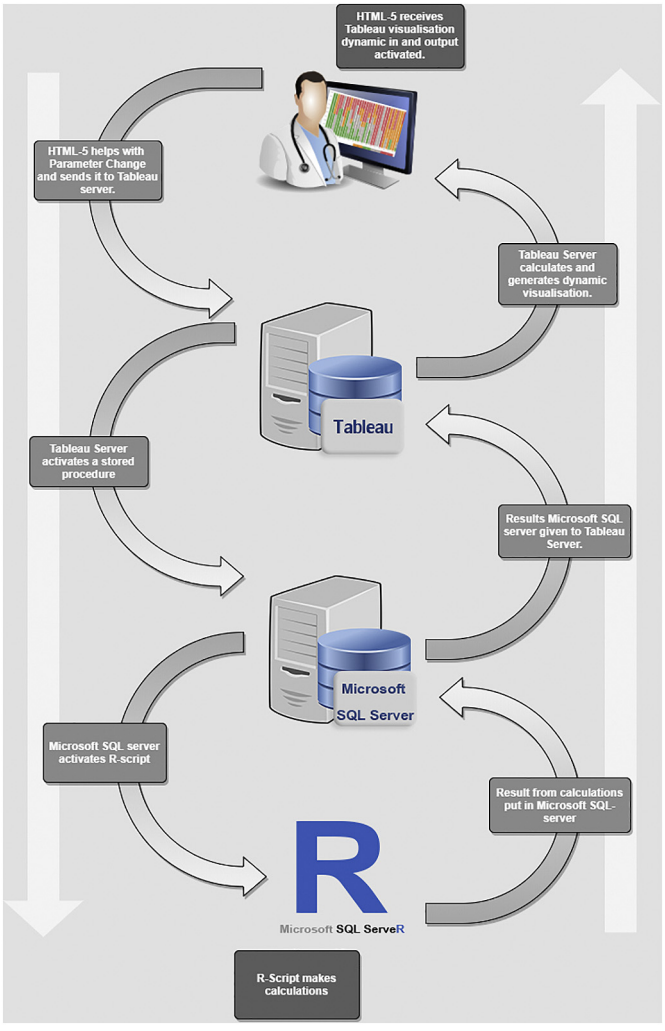

Fig. 1. Information technology structure.