Assessment of Dendritic Cell Therapy Effectiveness Based on the Feature Extraction from Scientific Publications

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Abstract: Dendritic cells (DCs) vaccination is a promising way to contend cancer metastases especially in the case of immunogenic tumors. Unfortunately, it is only rarely possible to achieve a satisfactory clinical outcome in the majority of patients treated with a particular DC vaccine. Apparently, DC vaccination can be successful with certain combinations of features of the tumor and patients immune system that are not yet fully revealed. Difficulty in predicting the results of the therapy and high price of preparation of individual vaccines prevent wider use of DC vaccines in medical practice. Here we propose an approach aimed to uncover correlation between the effectiveness of specific DC vaccine types and personal characteristics of patients to increase efficiency of cancer treatment and reduce prices. To accomplish this, we suggest two-step analysis of published clinical trials results for DCs vaccines: first, the information extraction subsystem is trained, and, second, the extracted data is analyzed using JSM and AQ methodology.

1 INTRODUCTION

Usually cancer patients are treated by radical removal of the tumor, radiotherapy or cytotoxic drugs. However, after surgical procedure many patients have a relapse because some cancer cells persist in the body. Use of radio- and chemotherapy does not always give the desired result. Efficacy of radiotherapy is restricted by the type of tumor and its location. Chemotherapy is often too toxic for the patient. Besides, the resistance of cancer cells to cytotoxic drugs can significantly increase in the course of chemotherapy. Consequently, despite extended treatment, relapses of the disease, including distant metastases are quite common. Thus, it is important to further develop methods to prevent tumor relapses.

Immunotherapy plays increasingly important role in cancer care. There are numerous data confirming its efficiency. Use of cell vaccines based on dendritic cells (DCs) is one of the most promising methods of anti-cancer immunotherapy (Shortman and Caux, 1997). DCs are the main type of the antigen presenting cells. They incorporate, process and exhibit the antigen on their surface membrane in the lym-

phocytes recognizable form. After that the lymphocytes become able to attack tumor cells. Monocytes (Zhou and Tedder, 1996) or hematopoietic stem cells (Welzen-Coppens et al., 2012) isolated from blood or bone marrow of the patient are used as starting material for DC vaccine preparation. These cells are cultured with cytokines to differentiate into DCs. DCs undergo maturation induced by loading with tumor antigens and are administered to the patients to stimulate cellular immune response against the tumor. Proteins extracted from surgically removed tumors, synthetic peptides or recombinant proteins can be used as tumor antigens for loading into DCs (Yannelli and Wroblewski, 2004). Hybrids obtained by fusion of DCs and tumor cells (dendritomas) may be used as a vaccine as well (Wei et al., 2006).

The necessity to isolate and process each patients own cells in vitro makes DC vaccines quite expensive and hard to standardize. It also makes it difficult to analyze the effectiveness of vaccination, because its efficacy is influenced by each patients individual features. It is thus essential to reveal patients characteristics critical for the success of vaccine application and to categorize the patients accordingly. Here we sug-

gest to solve this problem by extracting numerical and symbolic information from available sources including journal articles, theses, patients hospital records and clinical trial reports describing the use of DC vaccines and its analysis by machine learning methods.

2   RELATED WORK

Most published studies assessing the efficacy of DC-based vaccination are focused on one type of vaccine and one tumor form. It is true even for publications reviewing meta-analysis data.

There is quite an informative publication analyzing clinical trials of DC vaccines giving a systematic review and meta-analysis of clinical studies of 17 vaccines against prostate cancer and 12 vaccines against renal cancer (906 patients all together) (Draube et al., 2011). Such factors as the type of DCs used, antigen loading method, administration route, dose, adjuvants, toxicity and clinical response were evaluated. Additional parameters considered were patients age, sex, stage of disease, previous and concomitant treatment. Unfortunately, this paper summarizes only the results of using DC vaccines to treat two types of urological neoplasms.

Some papers analyze the dependence of the DC vaccines effect from the initial selection criteria applied to patient selection (Figdor et al., 2004; Murthy et al., 2009). Those criteria can include age, sex, stage of the cancer process, method of therapy, comorbidities, biochemical and hematological parameters of the blood, etc. Unfortunately, some selection criteria for a particular study look subjective and are not reasonably explained by the authors.

There are studies devoted to the information retrieval from medical texts (Aggarwal and Zhai, 2012) dealing with named entities extraction (drugs, diseases, etc.); finding of the connection between entities (genes and diseases, protein interactions, etc.); extraction of the correlation between time and cause. For text processing methods of syntactic, semantic and discourse analysis, co-reference resolution (Aggarwal and Zhai, 2012; Gaizauskas et al., 2003) are used, as well as regular expressions; contextual rules and templates compiled manually; classifiers (support vector machines, etc.). Currently, Deep Learning (Collobert et al., 2011) develops rapidly. Multilayer neural networks are the main tool for text analysis.

3   META-ANALYSIS METHODOLOGY

As pointed out above, it is important to separate patients into groups according to their characteristics essential for the vaccination success. It is obvious that the group formation should take into account nosology, because different malignant tumors have different degree of immunogenicity and different sensitivity to immunotherapy. The disadvantage of this approach is lack of data for some tumors. To avoid loss of data, we propose to use a two-level method for group forming. At the bottom level the classification into groups is based on the type of disease, for example "colorectal adenocarcinoma", "prostate cancer", "glioblastoma". At the top level malignant tumors are divided into five groups according to their origin and pathogenesis. Group I – "carcinoma and melanoma" includes tumors originating from epithelium or skin pigment cells. Group II – "sarcoma" embraces tumors from solid tissues such as osteosarcoma, rhabdomyosarcoma, etc. Malignant tumors originating from neural tissue such as neuroblastoma, glioblastoma and others constitute group III. Group IV – "hematological malignancies and solid tumors of the immune system" is represented by the diseases of hematopoietic and immune system such as leukemia, lymphoma, thymoma, etc. Group V includes tumors whose origin, etiology or pathogenesis differ significantly from the others.

Evaluation of the impact of DC vaccine preparation procedures demonstrated that there is at least one vaccine characteristic that might significantly affect the results of immunotherapy. This is DC vaccine valency, i. e. the number of antigenic determinants the vaccine was designed against. DC vaccine valency is determined by the substance that is loaded as antigen during vaccine preparation.

For the purposes of this study, we chose the clinical trials registry (http://www.clinicaltrials.gov) and information related to biomedicine retrieval machine http://www.ncbi.nlm.nih.gov/pubmed (Medline) as Internet sources of information about the results of clinical studies on the use of DC vaccines against cancer. These resources cover most of the data required worldwide.

We used keywords and word combinations "cancer", "tumor" and "dendritic cells" to retrieve the necessary data. When using Medline the restriction "clinical trial" was inputted. Sources of results of clinical trials were chosen with the help of text analysis. Data of randomized and other types of studies, regardless of their phase, were collected. Only studies with at least three participants with one of tumor types men-

tioned above were taken. Studies applying allogeneic or other types of non-autologous DCs were excluded.

Analysis of the registry of clinical trials revealed 387 registered trials of cancer treatment methods using DC vaccines. Unfortunately, only 20 of them provided information about the end results. The Medline search system produced 587 relevant sources of data related to malignancies treatment using DC vaccines. Of those 310 papers refered to the treatment of the first group tumors (carcinoma 148, melanoma 162); 17 articles described the treatment of the second group tumors (sarcomas); 38 articles were devoted to the treatment of brain tumors (III group); 103 articles concerned hematopoietic and immune system tumors (IV group) and two articles were about vaccination of patients with the V group tumors.

Besides general individual characteristics of the patient such as gender, age, race, that can always be found in the records of clinical studies, the characteristics of the tumor process and immunological status of the patient are of great interest. Conventional nomenclatures such as the International clinical classification of tumors by TNM (American Joint Committee on Cancer) allow characterizing the process of tumor development only within a nosological unit which it is not appropriate for this study. Therefore, we devised our own classification of tumor progression stages. The first stage is the absence of detectable tumor site. This stage is seen in patients who underwent radical surgery and were assigned immunotherapy using DCs vaccine to prevent relapse. The second stage is seen in patients with a primary tumor which can be combined with a limited number of local metastases. The third stage is a generalized neoplastic process with multiple distant metastases.

We ranked the immune status as "positive" and "negative". "Positive" immune status corresponds to the patient with the evidence of cell immune response. "Negative" immune status is characterized by negative immunoregulation such as increased number of regulatory T-cells or expression of immunosuppressive cytokines.

To evaluate the results of DC vaccine application it is necessary to formulate criteria of successful treatment. We concluded that the lifetime increase compared to a median of patient survival time without DC vaccine application, can be a valid criterion. This is the only possible criterion for the patients with the first-stage tumor (without visible tumor). Moreover, it allows not only qualitative, but also quantitative estimation of treatment efficacy. Unfortunately, the application of this criterion implies long-term follow-up of vaccinated patients. Consequently, the number of sources providing related information is limited.

We chose positive clinical response as the second criterion. That is complete or partial regression of tumor, as well as stabilization of the disease.

4 TECHNICAL MEANS OF META-ANALYSIS

To facilitate the proposed meta-analysis methodology, we are developing an informational analytical system. The system integrates modules that aim to automate all the essential steps of the proposed methodology: information gathering, information extraction and analysis of cause-and-effect relations.

4.1 Information Gathering

Information gathering is organized as thesauri-aided meta-search: user types a search query with the help of domain-specific vocabularies (e. g. MeSH, ICD etc.) and the system redirects this query to such public libraries of scientific texts as PubMed, Cochrane, etc. This leads to filling of a local publication database.

After an expert concludes that the local database is full enough they can launch information extraction module. The aim of this module is to convert unstructured or semi-structured information about patients and treatments presented in the documents found into the vector space representation.

The proposed module for information extraction implements a rather standard text mining pipeline: first, the documents are converted to plain text, then segmentation and tokenization, morphological analysis, syntax parsing, semantic role labeling, third-party information extraction algorithms and our information extraction methods follow. The engine is implemented using UIMA (Ferrucci and Lally, 2004), thus each processing step reads source data from and writes results to a unified graph-like data structure called CAS. CAS contains text and annotations. Annotations are program objects that are labelled spans of text. Annotations have attributes (properties) of various types and may refer to other annotations.

One of the peculiarities of our pipeline is that it incorporates Tabula library to extract tables from PDF documents (Nurminen, 2013). It's important because many papers contain information about patients written as tables. After Tabula extracts tables, the text in cells is aligned against the full text and the corresponding annotations are added to the CAS. Other incorporated tool is cTAKES (Savova et al., 2010).

To reduce the necessary manual labor amount we use on-line active machine learning paradigm: the overall process of analyzing the documents is split

into iterations, on each the system outputs the extracted information and asks the user to provide some feedback, i.e. answers to questions like "Is it a positive example of X?" and/or "Is this a positive/negative example of X because of Y". To efficiently analyze expert's feedback and generate the questions, we index all the CASes using a graph database. It's preferred, but not necessary to use an incremental learning algorithm. SVM and inductive rule builders support this (Cauwenberghs and Poggio, 2000).

The problem of information extraction is treated as a combination of binary classification problems: first, a classifier must determine, whether a token represents a particular characteristics; second, it must find mentions of patient groups (similarly to the first subproblem); last, it must link characteristics to these groups. Most of existing classification algorithms work with vector-space object representation, thus it's important to choose appropriate feature selection procedure. Currently, we experiment with information gain, Euclid distance between positive and negative examples and various graph traversal strategies for features extraction and selection. Classifiers being tested are VM, HMM, CRF, ProbLog, decision trees, neural networks (Collobert et al., 2011).

4.2 Feature Extraction

The information extraction step results in a summary table in which rows correspond to groups of patients and columns – to their features. Table 1 is an example of such a table. In most cases, it contains columns that identify patient groups (paper identifier/number of the group), describe diseases (via ICD-10 codes or verbally), present results of various analyses (e.g. tumor antigens), demographic information (gender, sex), type of vaccine used, loading technique and measures of outcomes (average survival time with and without treatment). Usually the summary table contains a few hundreds of columns. Additionally, to increase separability of classes, the binarization technique may be applied to this table. According to binarization, features with K possible values ($K > 2$) are replaced with K new features with only two possible values, indicating presence or absence of the corresponding value of the source feature.

To identify the set of significant features, the previously mentioned table is analyzed using inductive machine learning methods. To determ the effectiveness of specific DC vaccine types we choose JSM method (Anshakov et al., 1991). JSM method is an algorithm that allows discovering of cause-and-effect relations. Although it was extensively used in various areas, its applications are limited to only small-

scale problems (only about a few tens of features). To overcome this issue, we propose to preliminary select features using a more lightweight method, e.g. AQ (Wojtusiak et al., 2006). The idea of the proposed feature pre-filtering is that only those features that AQ (or other preprocessing method) chooses to build up the decision rules are forwarded to JSM method.

For this purpose, the table is represented as a matrix of feature values $A = \{a_{ij}\}$. In this matrix columns correspond features and rows - to theirs values:

$$p_j \rightarrow (a_{1j}, a_{2j}, \ldots, a_{nj}), \qquad (1)$$

and each group of patients (object) corresponds to it description

$$o_i \rightarrow (p_1 = a_{i1}, p_2 = a_{i2}, \ldots, p_m = a_{im}), \qquad (2)$$

where $p_j = a_{ij}$ is a characteristic of an object.

Continuous features are discretized as follows. The whole interval of feature values is divided into three subintervals: w_1 – low values, w_2 – medium values, and w_3 – high values. The system divides all patients into classes according to successfulness of the vaccination. As a result of learning, all classes are described using a set of characteristics (AQ-rules (Michalski, 1973; Wojtusiak et al., 2006)). Characteristic h_j is a disjunction of feature value intervals: $p_j = \bigcup_q w_q$.

We propose to treat the process of rules generation as an optimization problem that consists in finding a possibly optimal set of rules. However, classical optimization procedures cannot be applied, because of the large number of features and their values. So it is reasonable to use a genetic algorithm (GA). GA have been extensively applied to solving complex optimization problems with non-standard algorithmic assignment of functions, complex configuration of the admitted region, with multi-extremal functions, large number of variables, etc. (Goldberg, 1989).

We use a recently developed modification of the well-known GA - co-evolutionary asymptotic genetic algorithm (CAGA)(Sergienko and Semenkin, 2013). It has fewer parameters than the standard GA. It represents several asymptotic probabilistic GA that work in parallel and compete for a common resource - a number of individuals in the population, and share the best found solutions with each other. Base algorithms have an adaptive mutation operator and differ from each other by the selection criteria. Such a combination of algorithms make it unnecessary to choose the selection, recombination and mutation operators, which are individual for each discrete task.

Thus, we suggest to run an iterative process that uses CAGA to find the best rule that covers the maximum number of positive examples and uses the minimum number of characteristics. Examples that satisfy

Table 1: Example of structured information about patient groups extracted from scientific publications about DC trials.

Group	Disease	HLA	Vaccine	Load	T cell Ir.	SR. Before	SR. After
1/1	Melanoma IV	1	MAGE A3 (168-176) I	-	1	-	-
2/1	NSCLC III/IV	-	MAGE A3 (112-120) I	Indir 10	1	52	309
2/2	NSCLC III/IV	-	MAGE A3 (112-120) I	Dir 10	1	280	655
3/1	Glioma 3/4	-	OK-432 diff.	-	1	400	480

the found decision rule are not excluded and they are taken into account in subsequent steps. Within each iteration at least one new object should be covered. If two rules have the same length and coverage, the one that covers a greater number of examples of the original set is chosen.

An individual represents some rule which is encoded in a binary string as a sequence of characteristics. Since each feature has three values, a feature is encoded by three numbers (0 or 1), which are interpreted as the presence or absence of the corresponding feature value in the rule. If all feature values are equal to one, then the feature is insignificant and it should be excluded from rules during decoding.

Extracted descriptions of groups of patients are sparse and often miss some features. To deal with missing data, we assume that a rule covers an object if they don't contradict to each other: the rule must contain only values, which the object description either contains or misses. When covering positive objects there is one more condition: a rule has to include at least one the non-missing feature value.

Due to the data sparsity there can be a situation when a positive example is similar to a set of negative ones and there is no rule that separates them. This means that such set of objects has conflicts and therefore we first delete such conflicting negative examples from initial set before the rules learning.

We selected the fitness function as a weighted sum:

$$\alpha N_{init} + \beta N_{cur} - \gamma N_{gen} \to \max, \alpha \gg \beta \gg \gamma > 0, \quad (3)$$

where N_{cur} is a number of covered positive examples of the current set, N_{init} is a number of covered positive examples of the initial set, N_{gen} is a number of properties involved in the rule. The weights are defined once before running the algorithm so that the first summand makes the greatest contribution to the sum and the last summand – the smallest contribution. Such type of function allows to identify the rules that cover the largest number of examples to choose the smallest rule.

We evaluated our method on medical dataset MIMICII (Massachusetts Institute of technology, 2014). We chose two groups of patients with two different diseases (65 and 60 patients correspondingly)

and automatically constructed rules that allowed distinguishing these patients according to their features. We also compared our rules with rules obtained by original AQ-method. The results of the comparison are present in the table 2. The last column P shows which part of rules covers a large part of objects (at least one tenth of all objects).

Both methods were able to construct rules that cover all positive objects. Number of feature values in rules is almost the same in both cases. The following differences of methods should be highlighted. AQ-method generates less number of rules. However, only small part of these rules covers a large amount of objects. Thus, there are three rules in average (one tenth of all rules) that cover more than one tenth of objects. At the same time our method constructs a set of rules a bit larger, but there are more than twenty rules in average (more than a half of all rules), which cover more than one tenth of objects. Another difference is that rules generated by our method are significantly differ from each other, when rules of AQ-method are similar to each other and do not allow considering all valuable features, which are required for JSM-method.

4.3 Analysis of Cause-and-effect Relations

As a result of feature extraction, each group of patients is described with a set of rules containing only significant features:

$$\mathfrak{R}_k = \{R_{ki} | R_{ki} = \bigcap_j (p_j = \bigcup_q w_q)\}. \quad (4)$$

The set of features used to search cause-and-effect relations consists of all the features used in all the rules generated at the previous step. These cause-and-effect relations form the so-called fact base that explains why a certain case of DC vaccination is successful or not. Generation of causal hypotheses is performed using the JSM-method (Anshakov et al., 1991). Besides, objects of all classes are considered as the entire set of objects (positive and negative examples within the fact base).

JSM-method relies on the following assumptions:

Table 2: Comparison of rule sets obtained by our method and the original AQ-method.

	Number of rules	Length of rules	Covered objects (%)	P (%)
AQ-method	21–23	9–11	100	10–15
Our method	32–36	14-16	100	50–60

- *similarity hypothesis*: if descriptions of all objects with observable feature have only one common part, then this part is a cause of the feature;

- *differences hypothesis*: if descriptions of two objects are similar, except one part, and this part is present in the case where the feature appears, then this part is considered as a cause of the feature;

- *abduction hypothesis*: if a set of parts of the description explains a set of hypotheses, then these hypotheses are plausible.

JSM-method generates hypotheses about the cause of the target feature value in the form of conjunction of values for the class c_k. A set of hypotheses generated for characteristic h_g is reduced by the length and nesting. If a complex cause contains more than three properties, it is considered as not significant. Causes which are an extension of other ones due to the conjunction of the characteristics are also excluded from the set of hypotheses.

This method for cause-and-effect relations mining is used to analyze medical and psychological data and recommended by experts in these fields due to transparent and intuitive results (Blinova et al., 2003; Finn et al., 1996).

Finally, we can define a classification problem: given the features of a patient, disease and a DC vaccine, we need to determine whether this treatment will be successful or not. Let h_{DC} (the class label) be the feature that corresponds to the estimation of efficiency of a DC vaccine. The input feature set consists of properties identified by the JSM-method as causes of a certain value of h_{DC} feature.

5 CONCLUSIONS

Classification of patients with cancer on the base of numerical and symbolic information, extracted from scientific publications and other sources, is proposed in this article to increase the effectiveness of DCs vaccines application. Two-level division of patients into groups according to the type of disease and type of tumor is recommended. To justify such division we analyzed the registry of clinical trials and the Medline search system, found reliable information for different groups of patients and conducted an initial selection of parameters that have a core role in patient classification.

For further analysis of the retrieved information a combined method for machine learning is proposed. It combines the advantages of statistical and inductive analysis and has already proved its applicability for the analysis of clinical and psychological data.

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