ASYMS©-SERAT: A SIDE-EFFECT RISK ASSESSMENT TOOL TO PREDICT CHEMOTHERAPY RELATED TOXICITY IN PATIENTS WITH CANCER RECEIVING CHEMOTHERAPY

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Abstract: Patients undergoing chemotherapy want specific information on potential toxicities of their treatment. Such information includes what side-effects they are likely to experience, how severe these side-effects will be, how long they will experience them for, and the best ways of managing them. As well as improving the experiences of patients, information about potential side-effects may also be of significant benefit clinically, as patients who are 'at risk' of developing certain toxicities may be identified, facilitating more targeted, cost-effective interventions. This paper describes research that uses risk-modelling techniques for identifying patterns in patient side-effect data to aid in predicting side-effects patients are likely to experience. Through analysis of patient data, a patient can receive information specific to the symptoms they are likely to experience. A user-friendly software tool ASyMS©-SERAT (Advanced Symptom Management System-Side-Effect Risk Assessment Tool) has been developed, which presents side-effect information to the patients both at the start of treatment and reviews and monitors predictions with each new cycle of chemotherapy received.

1 INTRODUCTION

In this paper we discuss the development of a user-friendly software tool ASyMS©-SERAT (Advanced Symptom Management System-Side-Effect Risk Assessment Tool), designed to provide patients undergoing chemotherapy treatment with a personalised prediction of possible side-effects they are likely to experience. Prediction of possible toxicities is achieved through the use of risk modelling techniques, which facilitate a better understanding of how a patient's personal information, the chemotherapy regime they are undertaking, and any previously experienced symptoms (if appropriate) contribute to the likelihood of future symptoms occurring.

Section 2 provides the reader with an overview of the project; detailing the current state of symptom modelling, risk modelling and how the approach can be applied to prediction modelling. The methodology adopted is also discussed as well as the actual aims of our research. In Section 3 we present the software ASyMS©-SERAT, discuss possible ways in which the system might be used and show the type of prediction information which can be provided. We conclude with Section 4, discussing work-to-date and ways in which we hope to develop ASyMS©-SERAT in the future.

2 PROJECT BACKGROUND

2.1 Symptom Modelling

In the UK approximately 277,000 individuals are diagnosed with cancer each year (CRUK, 2003) and this figure is projected to significantly increase over the next decade (SEHD, 2005). A majority of these

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individuals are likely to receive chemotherapy treatment at some stage of their illness. The toxic effects of chemotherapy puts patients at risk of developing a number of side-effects, some of which can become serious and life threatening if not detected and managed early. Approximately 9-21% of patients receiving chemotherapy are hospitalised due to such severe treatment related toxicity (Chen-Hardee et al. 2006; Du, Osborne, & Goodwin 2002;Kuderer et al. 2006; Polednak 2004) and 10% of patients die as a result of them (Kuderer, Dale, Crawford, Cosler, & Lyman 2006).

The effective monitoring and management of symptoms in this patient group is vital. However, it is now recognised that symptoms in patients with cancer are often poorly assessed and managed (National Institute for Health, 2002). Factors such as inadequate patient provider communication (Cleeland et al, 1986), and poor symptom assessment (Cleeland et al, 1994) have been cited as being contributory factors. The recent changes to the organisation of cancer services may also contribute to the sub optimal management of symptoms. With the focus of care now being in the home and out-patient setting, patients are left to manage the majority of side-effects on their own without direct supervision from health care professionals; this may leave them feeling anxious and having lack of control over their illness and treatment (McCaughan & Thomson, 2000). Furthermore, patients with cancer often find the unpredictability and diversity of potential side effects difficult to deal with (Cohn 1982; Tierney, Taylor, & Closs 1992).

Patient education is therefore fundamental to effective symptom control. It is widely acknowledged that patients with cancer want information on how to manage the symptoms and side effects associated with their disease and treatment (McCaughan & Thompson 2000; Skalla, Bakitas, Furstenberg, Ahles, & Henderson 2004). However, they often report feeling overloaded with the wealth of information provided and as a result experience problems with retaining and retrieving it (Skalla et al. 2004). As a consequence, there have been calls for the provision of information on cancer therapies, which is tailored to patients' individual characteristics and needs (Skalla et al. 2004; Dikken & Sitzia 1998). Patients want more specific information on potential toxicities of treatment, such as what side-effects they are likely to experience, their severity, and duration and how to manage them (Skalla et al. 2004). The provision of such information is likely to make them feel more in control of their disease by knowing what to expect and how to deal with problems when they occur. Furthermore, it may prevent unnecessary worry and anxiety over side-effects that are less likely to arise (Skalla et al. 2004). Whilst not only having the potential to greatly improve the experiences of patients with cancer receiving chemotherapy, a more accurate prediction of potential side effects of such treatments, based on patients individual and disease related characteristics, may also be of significant benefit clinically. By knowing the likelihood of potential side effects occurring, patients who are 'at risk' of developing certain toxicities may be identified, facilitating more targeted and cost effective interventions, to those in greatest need and who are most likely to benefit. It may also guide clinicians in the selection of appropriate treatments for individual patients based on their characteristics and needs.

2.2 Risk Modelling

Within health care, there is increasing use of predictive models to identify patients who are most likely to experience specific disease and/or treatment related events. Relative to cancer care, such models have tended to focus on predictors of survival and life threatening toxicities such a febrile neutropenia (Chow, Harris, & Fung 2006; Donohue 2006; Lyman et al. 2005; Sanchez et al. 2006; Vigano et al. 2000). In relation to the prediction of symptoms, there is limited work that has been performed in this area, particularly in relation to the area of chemotherapy side-effects (Armer et al. 2003; Talcott et al. 2003; Poleshuck et al. 2006).

Risk modelling provides a powerful mechanism for identifying patterns in data and predicting what will happen in the future. A variety of techniques can be employed to analyse data and the results of such analysis can be used to provide likelihood information relating to the prevalence of similar data occurring in the future. This information can relate to the likelihood of specific data values occurring together, or perhaps the frequency with which whole records of information may occur again.

The potential for using mathematical techniques to identify risk is reinforced by their prevalence in the literature: Cowie et al (2006) discussed the use of Bayesian belief networks in aiding in dementia diagnosis, where patterns are identified in data from patients who are potentially dementia sufferers and such patterns used to help predict whether dementia is present; Werner and Fogarty (2001) developed mathematical models to allow simulation of future events based on past medical records. Using this technique, the occurrence of thrombosis was predicted in sufferers of collagen disease; De Toro et al (2003) used neural networks to predict hospital

mortality of patients in intensive care more accurately than traditional regression models; Dybowski et al (1996) successfully applied multi-objective optimisation to analyse electrocardiogram (ECG) traces to provide a non-invasive technique for diagnosing potential signs of atrial disease; García-Pérez et al (1998) use data mining and neural network techniques and Mani et al (1997) apply decision-trees and rule-based approaches to differentiate between different dementias types.

The risk modelling techniques available differ in the way in which the data is analysed, how much data the technique requires to make significant predictions, and how much information is revealed regarding the patterns that exist. In general, it is advisable to use a variety of different methods to ensure that as much prediction data can be obtained as possible.

2.3 Project Aims

In order to identify patterns in side-effects experienced by patients receiving chemotherapy, data was analysed with a view to answering the following key questions:

- Does the chemotherapy regime impact on the side-effects experienced?
- Can we predict later symptoms from the pattern of early symptoms?
- If side-effects are experienced in an early cycle does this increase the likelihood of experiencing the same side-effects in later cycles?
- Do some side-effects always occur together and does the presence of some symptoms make others less likely to occur?
- Does the severity to which a side-effect is experienced impact on the likelihood of that side-effect occurring again?

The principal aim of the project was to provide new patients with a prediction of side-effects they are likely to experience across all cycles of chemotherapy. The secondary aim was to provide patients with ongoing side-effect information. By monitoring their side-effects over a period of time, we hoped to provide up-to-date predictive information which is revised and reviewed (according to how their side-effects change) over the cycle of treatments. Currently, the study focuses on six symptoms associated with chemotherapy: mucositis, nausea, vomiting, fatigue, diarrhoea, and hand-foot syndrome.

2.4 Research Methodology

2.4.1 Data Collection

Thirty-three retrospective cases of patients with breast cancer undergoing chemotherapy have been used in the study. Risk modelling analysis was performed on this data in an attempt to answer the questions posed in Section 2.2. Current data collection is also taking place from three sites across Scotland, which will form a prospective data set consisting of forty patients. These patients have been diagnosed with breast cancer and are commencing adjuvant chemotherapy.

Data is being collected using a series of daily patient self-reporting paper-based symptom questionnaires collected throughout 4 cycles of chemotherapy. The daily symptom questionnaire is being used in addition to the clinical use of two existing questionnaires commonly used in practice to assess and grade chemotherapy related symptoms – the Common Toxicity (CTC) grading system (National Cancer Institute, 2003) and the Chemotherapy Symptom Assessment Scale (C-SAS) (Brown et al, 2001). This data will be used to further assess the accuracy of the risk-modelling tool.

2.4.2 Data Analysis

The data analysis performed uses both traditional statistical techniques and a class of more advanced, powerful techniques collectively known as 'data mining'. Data mining is task oriented, which means that analysis begins with the definition of a task and progresses through the use of data and software to develop a system for performing the chosen task. In this study, the task is to predict future symptoms from a combination of patient data and current symptoms. The pattern of symptoms experienced as a patient progresses through a chemotherapy regime is not random, and as such can be predicted. Data mining tools are designed to find the structure that allows such predictions to be made.

The data from this study was analysed in two distinct forms. One which treats the data as a time series on the assumption that there is a pattern in the way symptoms evolve over time (trends or cycles, for example) and the other being static, working on the assumption that the patient's initial state and the chemotherapy regime alone are sufficient to predict when and with what severity symptoms will occur. For the time series analysis, we used dynamic Bayesian networks, Markov models and a decompositional approach. For the static prediction the principal tools used were neural networks, cluster analysis, and Bayesian belief networks.

3 ASYMS©-SERAT

3.1 Introduction to ASyMS©-SERAT

The ASyMS©-SERAT tool will be incorporated into a mobile phone based, advanced symptom management system (ASyMS©-C) which has been developed to remotely monitor the side effects of chemotherapy in patients with cancer receiving chemotherapy (Maguire et al, 2005).

The ASyMS©-SERAT tool employs the use of risk modelling techniques to provide patients and clinicians with predictions of likely side effects. The prototype tool can be used to provide predictive information to both new patients, and those currently undergoing treatment. For new patients, the tool allows patient specific data to be entered and provides feedback as to likely side-effects (along with severity details) that will occur. As patients undergo treatment and side effects are monitored, the tool can measure these against the original prediction model. Prior to each cycle of treatment, a patient's predicted model can be reviewed and revised to provide a new predictive model if felt necessary.

The development of the tool has been split into two phases: Phase I which concentrates on the provision of information for new patients, and Phase II which provides information for returning patients part-way through their chemotherapy regime. To date, Phase I has been completed and it is envisaged that Phase II will be completed by February 2008.

3.2 ASyMS©-SERAT in Use

This description of ASyMS©-SERAT will focus on Phase I of the tool as this has now been completed. In Phase I of ASyMS©-SERAT, the tool uses information it has learnt from the data and combines this with patient specific information to predict the likely side effects a patient will experience over the course of their treatment. The patient can receive predictions relating to possible symptoms they are likely to experience in their first cycle of treatment as well as possible symptoms they are likely to experience across all cycles of treatment.

In Figure 1 we provide a sample screenshot depicting information about side-effects a patient may experience in their first cycle of treatment. From the textual scrolling area at the top of the screen, it is evident that this patient has a high chance of experiencing both nausea and fatigue during cycle 1, and some possibility of experiencing mucositis. The pie charts show how severe each of these symptoms could be. For example, about 17% of cases of nausea will be severe, about 33% will be moderate, and about 50% will be mild.

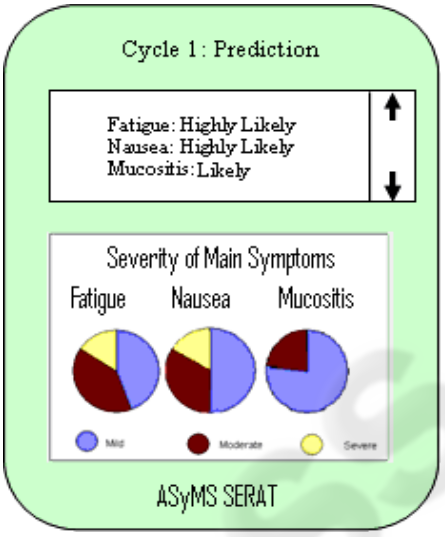

Figure 1: Screenshot of ASyMS©-SERAT showing likely side-effects in cycle 1 of treatment

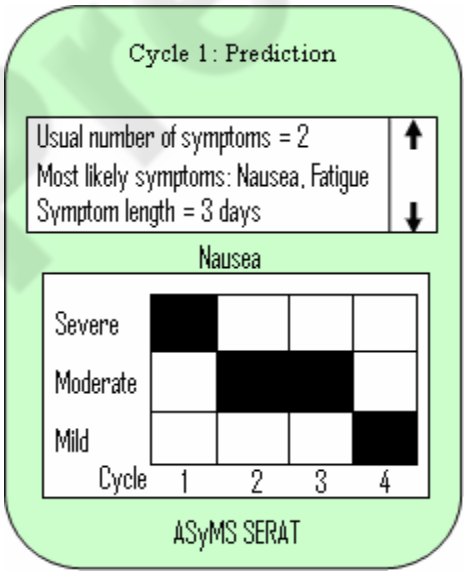

Figure 2: Screenshot of ASyMS©-SERAT showing predicted severity of nausea symptoms across cycles 1-4.

The screenshot in Figure 2 provides longitudinal information across all cycles. Such information can be used to inform the patient about likely patterns of symptoms over time. In the example shown, it is evident that although the patient is experiencing severe nausea in cycle one, this symptom will become moderate during cycles two and three, falling to mild by cycle four.

4 CONCLUSIONS AND FUTURE WORK

Although research on the project is still in its infancy and the ASyMS©-SERAT tool is very much a prototype system, initial results from the risk modelling analysis are very promising. From initial testing it would seem that through use of ASyMS©-SERAT, accurate, personalised predictions of possible side-effects can be made, providing patients with a more informed view of their treatment, and clinicians with the information required for preventative measures or management of side-effects to be applied where possible.

Once Phase II of ASyMS©-SERAT tool is complete, we hope to incorporate the tool in existing ASyMS© symptom management software. This complete symptom prediction and management tool will hopefully allow patients to feel more in control of their symptoms, knowing in advance what to expect, and how to manage the symptoms accordingly. A larger, more comprehensive evaluation of the ASyMS©-SERAT tool will be conducted as part of this work. We are currently in the process of applying for further funding to facilitate this next stage of the project.

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