SMART TRANSPLANTATION
Fever of Unknown Origin after Stem Cell Transplantation as a Model for a Knowledge-Based Decision Support System in Medicine

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Keywords: Human-Computer Interaction in Health Care, Usability of Medical Information Systems, Human Aspects of Future Technologies in Health Care, Cognitive Task Analysis, Usability Engineering, Stem cell transplantation, Decision support system.

Abstract: Public health care has to make use of the potentials of IT to meet the enormous demands on patient management in the future. Embedding artificial intelligence in medicine may lead to an increase in health care quality and patient safety. One possibility in this respect is the use of knowledge-based decision support systems which facilitate the practice of evidence-based medicine. Conditions for such a system are structured data sources to extract relevant data for the proposed decision. Therefore, the demonstrator “allo-tool” was designed. To develop the allo-tool a user-orientated process was applied and future users of the later software were integrated in each step of the development process. The concept of introducing a "Medical decision support system based on the model of Stem Cell Transplantation" was developed afterwards. The global objectives of the planned system are (1) to improve patient safety (2) to support patient autonomy and (3) to optimize the work flow of medical personnel.

1 INTRODUCTION

In many areas of human life, computer-based Information Technology (IT) has prevailed and has become essential for the coordinated and efficient organization of work flow. This offers numerous advantages for the future, but will also lead to problems for the people confronted with it. Especially in the field of health care, interaction between human beings and information technology is a sensitive subject. Physicians have immense reservations and apprehensions of being made the slaves of information scientists and of their programmed computer system. Nevertheless, medicine has to become more scientific in patient management. The importance of interdisciplinary advice and discussion which is a prerequisite for the best possible decision on a treatment strategy has to be reflected in the application of new information technologies.

Embedding artificial intelligence in medicine may lead to an increase in quality and safety and to a decrease in costs significantly. In the future, IT-systems are supposed to have the ability to extract the relevant knowledge to filter irrelevant information and focus on significant information and to present it available to the user. Inevitably, people working in health care will have to make use of the potentials of IT in order to meet the enormous demands on patient management in the future.

One possibility in this respect is a knowledge based decision support system which facilitates the practice of evidence-based medicine. The idea of medical decision support systems is not new. In the past, however, these systems have not become popular and utilized. The reason was not that the technology had failed, but that the implementation was inadequate. A prerequisite for success is that we understand "how medicine thinks" in order to be

Meixner G., Thiels N., Haschler I., Wicht A. and Klein U. (2008).
SMART TRANSPLANTATION - Fever of Unknown Origin after Stem Cell Transplantation as a Model for a Knowledge-Based Decision Support System in Medicine.
In *Proceedings of the First International Conference on Health Informatics*, pages 298-304

able to create a "decision-supporting", and not a "decision-making" system.

Decision support systems need an evaluation of their applicability and of their cost-benefit relationship as well as the evaluation of precision, quality, and effects of their recommendations. Against the background of the challenges mentioned above, the concept of introducing a "Medical decision support system based on the model of Stem Cell Transplantation", named allo-tool, was developed.

Whenever bringing a decision support system into clinical practice, one has to consider the possible harms caused by the system. Concretely this means to consider what happens if the system recommends a wrong decision or presents incomplete or inadequate information at the point of care to the physician. We therefore plan to integrate a feedback mechanism. In the case that a physician has the opinion that the system could recommend something wrong, he will submit an incident report to the maintenance team. In that way, the users (i.e. mainly the physicians) will retain control over the system and possible harm to the patients caused by the system will be minimized.

The global objectives of the planned system are (1) to improve patient safety (2) to support patient autonomy and (3) to optimize the work flow of medical personnel. It might lead to more efficient use of resources without detrimental effects on the relationship between physician and patient or on the physician's autonomy to decide. The allogeneic haematopoietic stem cell transplantation is extremely well suited as a model for this type of system because of repeating standard procedures, the well defined span of time required and the predictable recovery period as well as recurrent side effects after transplantation.

2 STEM CELL TRANSPLANTATION

Hematopoietic stem cell transplantation (HSCT) or bone marrow transplantation (BMT) is a medical procedure in the field of hematology and oncology (Korbling, 1986). It is most often performed for people with diseases of blood or bone marrow (Gratwohl, 2007; Goldschmidt, 2000). HSCT remains a risky procedure and has always been reserved for patients with life threatening diseases. Since the availability of stem cell growth factors, most hematopoietic stem cell transplantation procedures have been performed with stem cells collected from the peripheral blood (Montgomery, 2007). Most recipients of HSCTs are patients with leukemia or aggressive hematological tumors who would benefit from treatment with high doses of chemotherapy or total body irradiation. Other patients who receive bone marrow transplants include pediatric cases where patients have an inborn defect and were born with defective stem cells. Other conditions that bone marrow transplants are considered for include inherently diseases of the bone marrow. More recently non-myeloablative, or so-called "mini transplant," procedures have been developed which do not require such large doses of chemotherapy and radiation (Djulbegovic, 2003). This has allowed HSCT to be conducted in older patients and as a matter of principle without the need for hospitalization. There are two major types of stem cell transplantation maneuvers: Autologous HSCT involves isolation of HSC from a patient, storage of the stem cells in a freezer, high-dose chemotherapy to eradicate the malignant cell population at the cost of also eliminating the patient's bone marrow stem cells, then return of the patient's own stored stem cells to their body. Autologous transplants have the advantage of a lower risk of graft rejection, infection and graft-versus-host disease. Allogeneic HSCT, as the second type, involves two people, one is the healthy donor and one is the recipient. Allogeneic HSC donors must have a tissue type that matches the recipient and, in addition, the recipient requires immunosuppressive medications. Allogeneic transplant donors may be related or unrelated volunteers.

The number of performed HSCT, autologous and allogeneic, is increasing. Due to better anti-infective medication the life-threatening side effects of infectious complications are decreasing but they still remain as the main risk factor for life threatening side effects (Walker, 2007; Afessa, 2006).

Therefore one intention of the allo-tool is the improvement of patient safety through a decision support system for choosing an anti-infective therapy based on evidence based advices.

Bacterial, viral or fungal infections are severe side effects of high dose chemotherapy and stem cell transplantation and can result in life threatening complications. Infections are the most important causes of morbidity and mortality in patients undergoing allogeneic stem cell transplantation. That is why immediate anti-infective therapy in case of fever is mandatory (Afessa, 2006). Because of the resistance to widely used antibiotics and a shift of

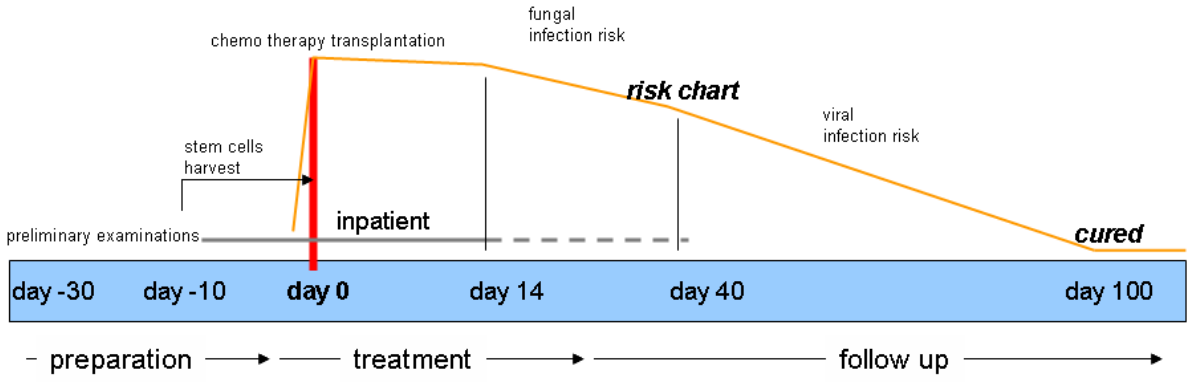

Figure 1: Risk chart graphic.

causative pathogens towards multi-resistant bacteria, anti-infective therapy remains to be a challenge. Beside this drug-interaction, kidney function, known allergies, the cause of fever and former anti-infective therapies needs to be included into the decision of the treatment of choice. Therefore the model of a decision support system was developed. The idea of programming and implementing such a system is not new. Attempts of this type had already been initiated in the Eighties (then called medical expert systems) (Shortliffe, 1975). In the past, however, these medical expert systems have not become popular and utilized. The reason was not that the technology had failed, but that the implementation was inadequate.

Beside this the support of patient autonomy through modern forms of communications like web-based access to specific patient data and the optimization of the work flow in the complex process of an allogeneic transplantation is the goal of the allogeneic tool “smartTransplantation”.

3 USEWARE ENGINEERING PROCESS

The level of acceptance and efficiency of a modern user interface are determined by the ease of use of the interface. Primary considerations in this evolutionary development process are always the requirements and needs of the user, for whom the user interface is being developed. The process consists of analysis, structural design, rough and detailed design, implementation, and evaluation (Zühlke, 2004). As a continuation of the analysis, evaluation occurs concomitantly to the development.

A risk chart (see Fig. 1) has been developed to get an understanding of the transplantation procedure. It explains the work flow of the stem cell transplantation in detail. The preparation of the analysis phase derived five different user groups. From these user groups ten different persons were chosen to be questioned to find out the tasks and needs of users for the later user interface.

After the questioning and characterizing, the collected data were compiled (Bödcher, 2007). Additional results included an analysis of weaknesses identified in the existing user interfaces and documentation of the “wish list” expressed by the users. Problems to be found within the analysis of the clinical situation for the stem cell transplantation were published.

Based on the task models of the different user groups, the use structure for the future user interface was developed. The modeling language *useML* (Reuther, 2003) was used in structural design. The result of the structural design phase is a platform-independent model and it provides the foundation for the later design phase. This model formed the base for the development of the prototype.

4 PROTOTYPE: ALLO-TOOL

The intention of the allo-tool is not only the optimization of the work flow in the complex process of an allogeneic transplantation, but also the provision of a structured platform for relevant data. This aim is reached by data integration from different existing information sources: clinical information system, drug information system and paper patient files as well as domain knowledge formalized in knowledge bases (described in more detail in chapter 5). The digitized aggregated data is displayed in a clearly structured way.

The tool shall be able to extract medical information from different sources, structure the

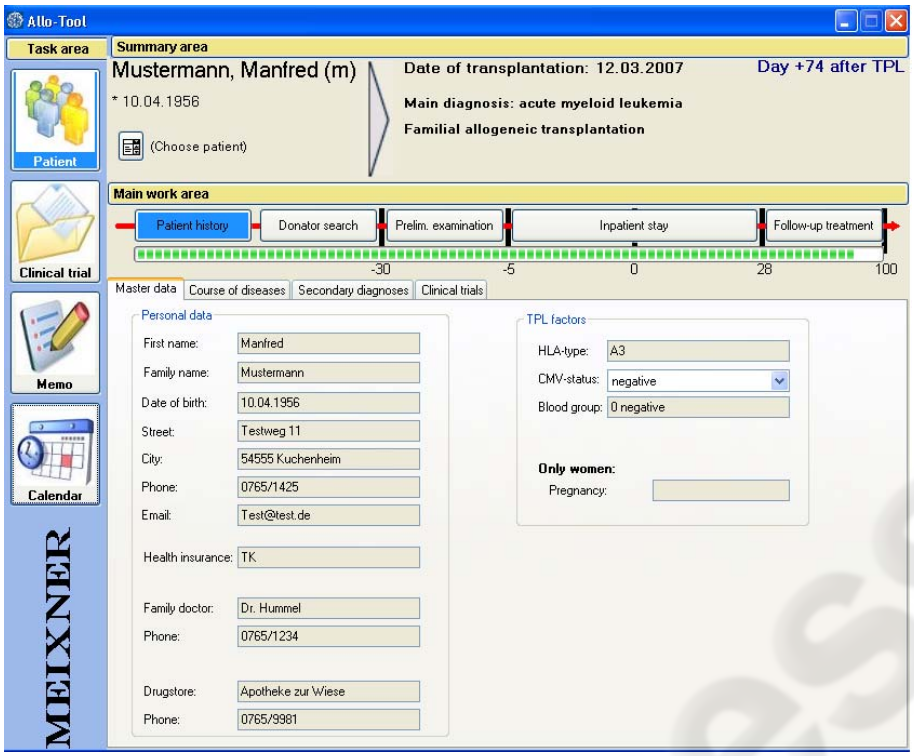

Figure 2: Patient history screen in the detailed view.

information and automatically generate discharge letters and further documents, e.g. drug plans.

Each user group is able to work consistently with the allo-tool. The tool consists of four main views: calendar, memos, clinical trials and patients. The memo view consists of a text field, where the user has the possibility to take notes. In the clinical trial view the user is able to administrate information about current clinical trials.

For allogeneic transplantations information about conditioning, transplantation, immunosuppression, GVHD prevention (graft versus host disease) and donor lymphocyte transfusions are stated within these clinical trials.

According to the work flow of an allogeneic transplantation, the detailed patients view consists of five different chronological parts in the main work area of the tool: patient history, donator-search, preliminary examinations, inpatient stay and follow-up treatment. These five parts are clearly separated phases in the time line of an allogeneic transplantation (see Fig. 1). The graphical representation of a time line (see Fig. 2) enables physicians to have a better understanding (Norman, 1990) of the current date according to the complex process of an allogeneic transplantation. The tool supports physicians in keeping deadlines according to a physical examination time schedule.

The patient's history phase (see Fig. 2) consists of a structured overview of the patient's master data. In the course of diseases previous examinations and medical results are displayed in a table view. Secondary diagnoses are an important part of the decision supporting system and help to minimize adverse effects.

The preliminary examination phase contains information about the accomplished examinations according to the physical examination time schedule. The results of external examinations are entered into the clinical information system. The allo-tool shall be able to extract the results of external examinations.

In the phase of hospitalization, the patient receives high dose chemotherapy and some patients a whole body irradiation. After that the allogeneic stem cell transplantation is performed. During the whole phase patient data (e.g. vital signs, blood counts or organ functions) are monitored very closely. Beside others, one important task of the attending physician is to administrate drug plans.

Via an implemented interface, physicians are able to use an existing drug information system (Kaltschmidt, 2004; Pruszydlo, 2006).

In the follow-up phase the physician is reminded to accomplish examinations according to the physical examination time schedule. The time schedule consists of a large number of physical examinations and complex execution logic. The prototype transfers the execution logic from the physicians to the software.

Patients in the follow-up phase have the possibility to access test results via internet and can directly communicate with their allocated physician via email. This will be reached by developing a web-based access for patients. Patients will have the possibility to view their own data (e.g. blood test results, X-ray photographs). Test results, which can be viewed by patients over internet are evaluated and released by their allocated physician. Patients in the follow-up phase have to control e.g. blood pressure values. They can measure blood pressure on their own and email the results over the web-based access directly to their allocated physician. So patients don't have to call the hospital via telephone or have to visit the hospital on their own.

5 KNOWLEDGE-BASED SUPPORT

In the future, physicians will be supported by a knowledge-based system with data mining capabilities. The detailed functionality is explained in the following.

Monitoring and interpretation of several parameters such as vital signs or laboratory results will be one main function of the knowledge-based system component. The system thus detects specific clinical situations and pushes unsolicited warnings or reminder and starts the according work flow.

In everyday clinical practice physicians are often faced with an information overflow rather than a lack of information, they have to spend valuable time in looking for relevant findings. To reduce this time a "Semantic Information Extraction" is provided. The system looks for findings in the patient's history which could fit into the context of the current clinical picture. Furthermore, it visualizes the classification of the findings, which has previously to be provided by a physician: "abnormal", "no abnormality", "unclear". So the physician gets a clearly arranged listing of relevant findings matching the current issue.

For a defined amount of clinical pictures, therapy and diagnostic recommendations are provided. These recommendations are on the one hand based on so-called domain knowledge which is patient-independent knowledge on e.g. diseases or processes. Domain knowledge will mainly derived from clinical practice guidelines (CPG) or in-house standard operating procedures (SOP). On the other hand they are based on available patient data such as current parameters as well as the patient's general data (if any parameters are missing or out of date, the system will ask the user to enter these), the system should give exact medication and dosing recommendations. Once the system has generated a recommendation, it will also provide the user with a reasonable explanation. In this context it may also be helpful that the user is guided to external knowledge resources, which match the current clinical picture, such as local SOP-documents, relevant study protocols or other medical knowledge bases, if further information is requested.

Recommending a (drug) therapy at first requires a knowledge base which encapsulates the SOPs and the guidelines' knowledge. The process of formalizing guidelines and SOPs is a challenging and time-consuming task (Kaiser, 2007). We will try to build a semi-automatic, peer-reviewed process, i.e. the system will try to import the unstructured material and recognize as much structure as possible. In the next step a specially trained medical professional will then review and complete structural or semantic issues. Afterwards, another medical professional will review the work of the first one to ensure high quality of the formalized knowledge.

Once the therapy decision was accepted and started, the system supports the medical staff by monitoring not only the over-all treatment work flow, but also the flow of the specific therapy. Concerning the over-all treatment work flow, the system should give reminders or warnings if scheduled diagnostic procedures (e.g. ECG) are not done or assigned yet or scheduled medications (e.g. antibiotic prophylaxis) are not ordered. Regarding the therapy monitoring, the system should detect if a patient does not respond to the treatment (e.g. patient remains febrile) and recommend necessary steps and/or alternative therapies as well as indicated diagnostic procedures. On the other hand, the system should detect if a therapy was apparently successful and recommend further steps (e.g. to stop antibiotics and to start a prophylaxis again). In this context the system presents - as already mentioned before - reasonable explanations and guides the user to external knowledge resources if requested.

As medical knowledge is subject to ongoing changes, the knowledge base has to be maintained regularly. Changes can be triggered either by external factors (e.g. update of a guideline) or by internal factors. We therefore need a user feedback mechanism which enables a physician to mark a system's decision as potentially wrong. The user

feedback has to be analyzed and the need to change the knowledge base has to be assessed. All changes to the knowledge base must be carried out within a "bullet-proof" process like the one described above.

A critical issue when it comes to the implementation of decision support systems is user compliance. In our environment we face mainly physicians as users, but also patients in an advanced state of the software (e.g. test results via web-based access). We have to ensure usability of the tool (as described earlier) and ensure that physicians get a benefit from it. The patients are most likely to do everything to improve their therapy outcome because of their severe illness.

One reason why decision support systems often do not prevail in clinical practice is poor work flow integration (Bates, 2003). Since our software will cover the SCT-treatment process as a whole we can map the practical work flow. Physicians will more likely use a decision support system if they see a clear benefit from it. This means mainly time-saving as well as convenient access to all relevant information.

Because the decision support system will be seamlessly embedded as a component into the allo-tool, we can reach an optimal solution to this obstacle. All of the knowledge-based features we presented above will appear within the current work flow context. We provide the medical user with only the information he or she needs at a given clinical situation. Therefore we can expect a reasonable time saving for the users. By ensuring that we do not miss relevant information on the other side, we may raise quality of treatment and patient safety.

6 CONCLUSIONS

It is incontestable that people working in health care will have to make use of the potentials of IT in order to meet the enormous demands on patient management in the future. Beside this the quality of work can be supported by intelligent software which is able to extract, rate and provide the user with relevant data. Not least patients require more autonomy of their own health information data. To meet this challenges the demonstrator of the allo-tool was developed.

Time consuming data search, redundant information and vast numbers of needed software applications are reduced by displaying all data in one tool. User interfaces, which are designed in close relationship to known software products, developed with the support of different users during the whole process and consulting of usability experts facilitate an easy-to-use application. Time schedules, reminder of deadlines and coherent information about study procedures enable medical staff to work efficiently. Taking these analysis results as a basis, conditions for a medical decision support system are accomplished. In order to meet the exploding number of scientific perception, decision support systems are needed in the future to maintain the quality of medical decisions.

Through web-based access to selected health information, patients obtain more autonomy and responsibility. Summarizing the potentialities of the planned allo-tool, the goals mentioned at the beginning, (1) improvement of patient safety (2) support of patient autonomy and (3) optimizing the work flow of medical personnel are illustrated. Studies to evaluate these potentialities are needed to prove these advantages of the allo-tool.

ACKNOWLEDGEMENTS

This work was supported by the Gottlieb Daimler- and Karl Benz-Foundation.

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