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Outpatient Chemotherapy Planning: a Literature Review with Insights from a Case Study

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With an ageing population and more efficient treatments, demand for cancer care is increasing. Therefore, hospitals need to find ways to improve their operational efficiency for cancer care. In this article, we review the contributions in the operations management and operations research (OM/OR) literature that address the planning of outpatient chemotherapy, one of the main treatments for cancer. The distinctive characteristics of outpatient chemotherapy are highlighted. In particular, the interdependence between the administration of chemotherapy drugs in the outpatient clinic and drug preparation in the pharmacy is pointed out. This makes outpatient chemotherapy planning a multiple department challenge where coordination is essential to the global performance of the system. The modeling challenges induced by this interdependence and by the clinical dimension of chemotherapy are presented. Finally, a case study is performed to confront the literature with the reality of a hospital. Important gaps in the literature are outlined, such as the lack of studies taking an integrated, systemic perspective on this multi-department issue.

Keywords

Chemotherapy, outpatient clinics, multi-department, healthcare management, pharmacy

1. Introduction

Cancer is a major health issue. 8.2 million people around the world died from cancer in 2012 (Ferlay *et al.* 2015). Direct costs for cancer care are expected to reach $173 billion in 2020 in the United States (Mariotto *et al.* 2011). Chemotherapy is one of the main options for treating cancer. It can be prescribed as a standalone treatment, or in parallel or in sequence with radiotherapy or surgery. Chemotherapy is mainly delivered by outpatient clinics. Outpatient cancer care accounted for 63% of total cancer care costs between 2001 and 2005 in the US (Tangka *et al.* 2010), and its cost is rising fast: from $25.5 billion in 2001 to $43.8 billion in 2011 in the US (Soni 2014). These figures show that cancer is a major issue, and outpatient chemotherapy is a strategic element in cancer care: its use increases and its cost is rising even quicker.

At the same time, healthcare systems are under financial pressure. Demand is rising but national budgets are not rising as fast (OECD 2013). Therefore, healthcare systems need to increase their efficiency: provide care to a higher number of patients without increasing their budgets in the same proportion. Finally, higher attention is currently given to patient satisfaction than before. Quality of care and patient-centered care are two central concepts for contemporary healthcare systems. Operations management and operations research (OM/OR) have long been involved in this evolution of healthcare systems towards this triple aim of "care, health, and cost" (Berwick *et al.* 2008). For instance, quantitative analysis of hospitals go back to the 1960's (Fetter and Thompson 1965), and today, the literature on modeling, analysis and simulation in healthcare is expanding at a rate of about 30 articles a day (Brailsford *et al.* 2009). In this context, focused reviews are needed to understand specific issues in healthcare management science.

From the point-of-view of OM/OR, outpatient chemotherapy shows a number of particularities. Many studies have been published on outpatient scheduling (Cayirli and Veral 2003) and hospital patient flows (Bhattacharjee and Ray 2014). However, outpatient chemotherapy is somehow in-between. It is not a simple consultation: the patient receives a treatment which may last as long as six hours. This treatment has to be prepared in the pharmacy. Therefore, outpatient chemotherapy requires the coordination of different services inside the hospital to provide the right treatment to the right patient while minimizing the costs and the patient waiting time. Outpatient chemotherapy is also different from outpatient surgery: patients require intermittent attention from medical staff, which makes it a coupled operations issue when it comes to planning. Finally, the presence of target dates for appointment planning, and the limited tolerances regarding their respect is another distinctive characteristic of outpatient chemotherapy. To the best of the authors' knowledge, no review exists on outpatient chemotherapy planning. Yet, the rising number of articles shows that this subject is gaining momentum. In this paper, we describe and discuss the distinctive features of outpatient chemotherapy planning studied in the OM/OR literature.

The orientation is towards application and implementation of OM/OR models and recommendations in practice, which is an important challenge in healthcare OM/OR studies (Proudlove *et al.* 2006, Brailsford and Vissers 2011). The literature is thus reviewed and synthesized from this angle. To go further and to put the literature into perspective, a case study is also introduced. The objective is to assess how the literature covers different organizational structures and takes into account the associated challenges. The situation of a French general public university hospital is presented. This case study illustrates that relationships and interdependences between departments are insufficiently addressed in the literature. For instance, more attention needs to be paid to the interdependence between the pharmacy and the outpatient clinic. In the literature, most articles study integrated cancer care centers, and only one paper describes a hospital with a centralized pharmacy from a systemic perspective, encompassing both the pharmacy and the outpatient clinic. However, we show that the case of general hospitals with centralized pharmacies justifies specific studies because of the close relation between the two departments. This case is representative of many European hospitals. The discussion highlights areas for future research on outpatient chemotherapy as a multi-department system and underlines the insufficient knowledge available on patient satisfaction predictors.

The rest of the paper is organized as follows. In Section 2, the method for identifying relevant articles is presented. Section 3 provides an overview of the clinical side of chemotherapy and the care process. Section 4 covers the organizational characteristics of outpatient chemotherapy. Section 5 deals with modeling issues. Three specific sources of complexity are developed: the coupled operations issues, the tolerances for treatment planning and the uncertainty on patients' status. In Section 6, a case-study is presented which serves as a basis for discussing the literature and confronting existing papers to current hospital practice. Section 7 discusses new directions for research. The paper ends with some concluding remarks.

2. Literature Review Procedure

To identify relevant articles, the *Web of Science* database was searched with the following combination of keywords: (*outpatient* OR *ambulatory* OR *pharmacy*) AND (*oncology* OR *chemotherapy* OR *cancer*) AND (*plan** OR *schedul** OR *simulat** OR *optimiz**). This first step generated 3,587 results. Keeping only articles in English reduced the number of results to 2,918 articles. Research areas were then refined to keep only *Operations Research & Management Science* and *Health Care Sciences & Services*. The resulting list contained 1,215 articles. The authors read the 1,215 titles and abstracts with the following criteria:

- Keep only articles which address chemotherapy administration (and not only medical consultations in oncology, which is similar to appointment scheduling, e.g. (Santibáñez *et al.* 2009)).
- Keep only articles that include at least one quantitative OR model for decision support (even when the quantitative model is used in combination with other, qualitative, techniques, e.g. (Baril, Gascon, Miller, and Cote 2016)). Therefore a paper such as (Baril, Gascon, Miller, and Bounhol 2016), where a case study on outpatient chemotherapy illustrates a methodological proposition on combining work sampling and simulation to obtain more realistic simulation models, is excluded as no operational objective is presented.
- An exception is made when the implementation of a quantitative OR model is developed in a separate paper (Mazier *et al.* 2010, Kergosien *et al.* 2011), or when a "qualitative" article describes a complementary part of an OR/OM intervention, e.g. (van Lent *et al.* 2009, Masselink *et al.* 2012).

This process resulted in a set of 11 articles. The references cited in these 11 articles were analyzed. In addition, articles citing these 11 articles were also screened, using *Google Scholar* and the *Web of Science*. 14 additional articles were included thereafter. As a result, 25 relevant papers are referenced in this review.

3. Background: Introduction to Outpatient Chemotherapy

Before moving to operations management issues of outpatient chemotherapy, we briefly describe in this section some clinical aspects of chemotherapy regimens. We also provide some elements on its standard care process.

3.1. Clinical Elements on Chemotherapy Regimens and Cures

Various types of treatment are possible against cancer. In chemotherapy, a drug or a combination of drugs is used to attack cancer cells. Chemotherapy administration is organized based on a chemotherapy regimen. A chemotherapy regimen is a set of cures. In each cure, a combination of drugs is administered to the patient by injection or intravenous (IV) infusion. Then, there is no intervention for a specified amount of time, after which a second cure is administered. Examples are provided for stage III colon cancer (Schmoll *et al.* 2006):

Regimen 1 (XELOX):

3-week cycle: Day 1: oxaliplatin 130 mg/m² 2-hour IV infusion

Day 1 to 14: oral capecitabine 1000 mg/m² day 1 to 14

Repeat for 8 cycles (24 weeks total treatment)

Regimen 2 (Mayo Clinic regimen):

4-week cycle: Day 1 to 5: leucovorin 20 mg/m² rapid IV infusion and then FU 425 mg/m² IV bolus

Repeat for 6 cycles (24 weeks total treatment)

Regimen 3 (Roswell Park regimen):

8-week cycle: Day 1 of weeks 1 to 6: leucovorin 500 mg/m² 2-hour IV infusion then FU 500 mg/m² IV bolus

Repeat for 4 cycles (32 weeks total treatment).

In Regimen 1, the patient will come to the hospital every three weeks to receive oxaliplatine in a 2-hour IV infusion. She will then take oral capecitabine, which does not require her to come to the hospital, for 14 days. She will then have a break for a week, and start again with oxaliplatine. This cycle is repeated eight times. At the end of the cycles, the efficiency of the treatment is assessed, and a new regimen can be decided. The state of the patient is also monitored between cures as chemotherapy can have severe side-effects.

These three examples show that chemotherapy regimens vary in terms of total duration, cycle duration, administration mode (oral, IV infusion, IV bolus – injection), infusion duration, etc. For all treatments, the prescriptions must be rigorously followed. The objective is to deliver the right dose with the appropriate intensity (dose per unit of time) so that the tumor is effectively attacked. Higher doses lead to better response rates (Frei and Canellos 1980), and lower dose intensity decreases treatment effectiveness (Lyman 2009).

3.2. Standard Care Process Organization

Chemotherapy administration (injection, infusion or oral administration) is only one part of the organization of chemotherapy. Other elements need to be taken into consideration: (i) consultations, blood tests and drug preparation; (ii) the involved capacity in terms of human and technical resources. These two elements are described next.

Process

Figure 1 lays down the steps of the patient pathway for a chemotherapy session. It shows that blood tests are performed before each session in order to ensure that the treatment can be safely administered. The blood test results are reviewed and the patient is examined by an oncologist. If the patient’s condition is adequate, the oncologist prescribes the drugs. This prescription is thereafter transmitted to the pharmacy which can start preparing the drugs.

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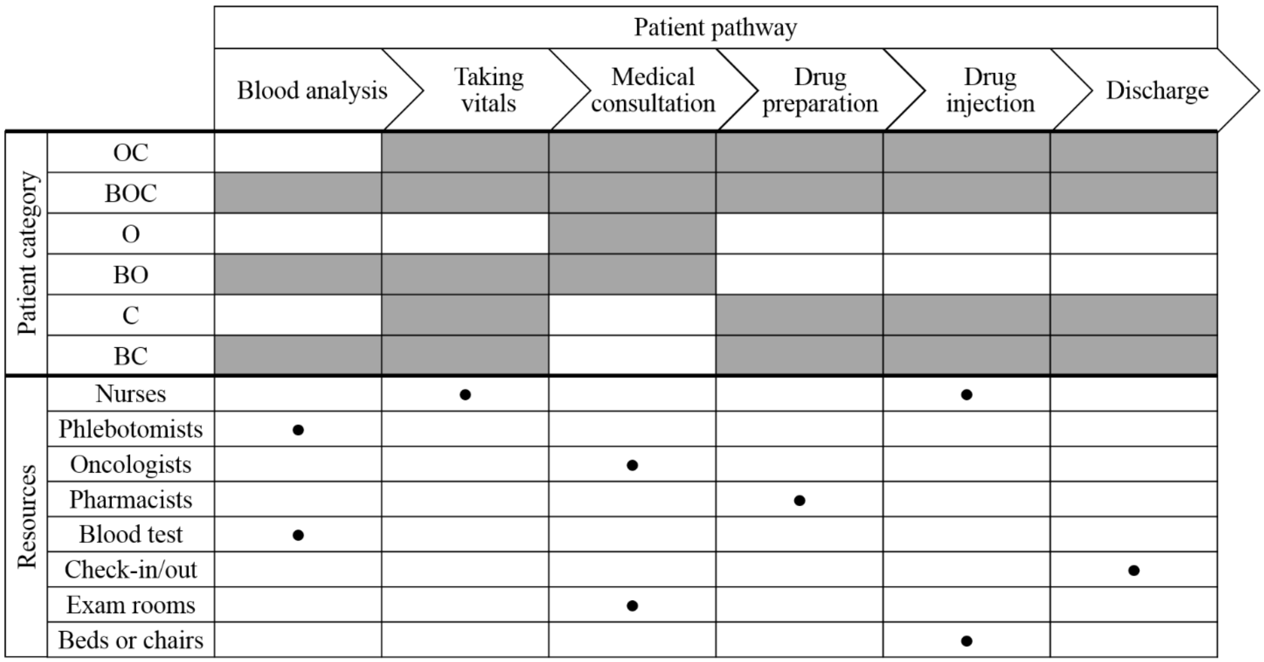

Fig. 1 Patient pathway for outpatient chemotherapy with patient categories and resources

However, all the steps of the process are not performed each time a patient comes to the outpatient department. Some patients don't need blood tests on a specific day, e.g. because they come for several consecutive days. For the same reasons, some patients don't get an oncologist appointment and go directly to chemotherapy administration. Liang et al. (2015) distinguish three categories: OC – oncologist appointment and chemotherapy, O – oncologist only, C – chemotherapy only. An additional distinction can be made on whether the patient requires a blood test or not, resulting then in 6 categories: OC, BOC, O, BO, C, BC. This classification is shown on Figure 1.

Resources

To perform the activities of the care process, the following resources are considered in the literature: nurses, phlebotomists, oncologists, pharmacists, blood test capacity, check-in/out receptionists, exam rooms and beds or chairs. Nurses usually perform a wide range of activities. They welcome the patient, take her vitals, draw blood samples, set up the intravenous infusion and follow-up on the patient during the infusion. They also perform indirect tasks like scheduling patients (Blay *et al.* 2002, Baril, Gascon, Miller, and Bounhol

2016). Phlebotomists are responsible for drawing blood samples (although this is sometimes done by nurses). Oncologists consult with the patient before the actual drug administration and they are responsible for drug prescription. Depending on their status, they may also have teaching and research activities. Oncologists could be further subcategorized as “full” doctors or interns. Pharmacists and their assistants are responsible for mixing chemotherapy drugs. They work in a subsystem, the pharmacy, where drug preparation is planned and performed. Blood test capacity represents the lab’s capacity to process blood samples. The lab can be either dedicated to the chemotherapy department or a general lab for the hospital. Check-in and check-out receptionists welcome patients and see them before they go home. They don’t perform medical tasks. Exam rooms are for doctors to consult with their patients. Beds or chairs are for chemotherapy administration: each patient needs one during drug injection. Figure 1 maps the involved resources for the various process steps. Although the process steps and resources are standard, their implementation can differ from one hospital to another. For instance, some steps can be performed outside the hospital, in particular blood tests. The next section describes these options, the decisions involved, and the Key Performance Indicators (KPIs) associated to the process.

4. Management of Chemotherapy Production and Administration

Concerning the organization of outpatient chemotherapy, three different aspects need to be investigated. The first is the organizational variants, i.e. the main options that can be taken in such systems. The second important notion is the decisions that managers have to make to plan outpatient chemotherapy at the strategic, tactical and operational levels. The last aspect deals with the choice of the KPIs to measure the system’s performance.

4.1. Organizational Variants

Although the clinical aspects of chemotherapy are universal, the practical organization of outpatient chemotherapy delivery varies from one hospital to another. These variants do not change the process as described in Section 3.2, but they modify its chronology (some steps can be performed days before treatment) and its operational management (e.g. with additional constraints on resource management). The various options as well as their corresponding risks and advantages are summarized in Table 1.

Table 1 Options for outpatient chemotherapy delivery

	Options	Advantages	Risks
Blood test	Chemo day in-house	Streamlined process Patients come only once	Patients wait Sensitivity to equipment failures
	In-house on previous day	Reduced waiting time on chemo day	Patients must come two days in a row
	In external lab on previous day	Reduced waiting time on chemo day Freed hospital lab capacity for other (more urgent) analysis	Poor hospital-lab coordination leads to a lost advantage and is time consuming
Drug preparation	Chemo day	Certainty on patient status: no wasted drugs	Patients wait Sensitivity to equipment failures
	Previous day	Drugs ready on patients' arrival if consultation is still on chemo day	Wasted drugs
	Mixt	Reduced waiting times Less wasted drugs than 100% on previous day	Patients with expensive drugs wait Still some wasted drugs
Oncologist consultation	Chemo day	Patients come only once	No early confirmation on patient status: patients wait drug preparation
	Previous day	Less waiting time because drugs can be prepared in advance Possibility to start chemo earlier	Patients have to come two days in a row
Nurse-patient allocation	Functional	Pooled resources: optimized utilization	Less possibility for patient-nurse connections
	Primary	Better patient-nurse connection	Lost productivity if the nurse's schedule cannot be filled

The first difference is that in some hospitals, blood tests are done on the day before treatment (Dobish 2003), either in the hospital or in town-based facilities, outside the hospital or treatment center (Sadki *et al.* 2013). Therefore, the blood test capacity can be assumed to be infinite for the hospital. It is however uncertain that test results will be transmitted on time prior to the patient's appointment at the treatment center. Similarly, oncologist appointments can take place one day before chemotherapy (Dobish 2003). The reason is that the preparation time for some drugs is too long such that the patient's appointment needs to be scheduled on another day (Masselink *et al.* 2012). Finally, there are various ways for the assignment of nurse activities. A patient can be allocated to a nurse for her whole treatment, or she can be allocated to an available nurse each time she attends the treatment center. These two options are called "primary care delivery model" and "functional delivery model" (Liang and Turkcan 2015). Some authors don't assign patients to nurses but rather match patient activities to available nurses, e.g. for the same patient the transfusion is set up by nurse A, but follow up during the infusion is performed by nurse B because nurse A is busy with other tasks (Hahn-Goldberg *et al.* 2014).

4.2. Decisions for Outpatient Chemotherapy Planning

Planning decisions in healthcare can be classified into strategic, tactical and operational decisions (Hulshof *et al.* 2012). For outpatient chemotherapy, all three levels have been tackled in the literature. A summary of all decisions tackled in the literature and the related references is given in Table 2.

Strategic Planning

Capacity dimensioning issues and facility layout are the only aspects of strategic planning addressed specifically for outpatient chemotherapy. This may be because strategic aspects such as geographic coverage and access are treated as part of wider cancer policies in public health and health policy journals rather than OM/OR research journals. Nurse staffing, chair/beds dimensioning, and doctor staffing are the three main issues considered (Matta and Patterson 2007, Yokouchi *et al.* 2012, Woodall *et al.* 2013, Liang and Turkcan 2015, Liang *et al.* 2015). In addition, one study analyzes lab capacity and pharmacy capacity (Baesler and Sepulveda 2001) and another evaluates new investment in a pharmacy chemotherapy hood and resource allocation for drug delivery (Lu *et al.* 2012). Only one article tackles facility layout (Sepúlveda *et al.* 1999). Finally, one article considers the opportunity to open a focused outpatient clinic for breast cancer patients alongside a general chemotherapy clinic for other patients (Vanberkel *et al.* 2010).

Tactical Planning

The first decision concerning resource planning is medical planning, where the weekly consulting periods of oncologists are defined for a year (Sadki *et al.* 2013). The other decision addressed in the literature is appointment scheduling, where the rules for scheduling patients are defined (rather than the mechanisms for allocating a specific patient to a specific timeslot, which is an operational decision) (Sepúlveda *et al.* 1999, Yokouchi *et al.* 2012, Huggins and Pérez 2014, Baril, Gascon, Miller, and Cote 2016). Finally, one article addresses process reengineering (Baril, Gascon, Miller, and Cote 2016). In the pharmacy, tactical decisions address the issue of advanced preparation. A policy must be defined to state which drugs can be prepared in advance, and which drugs can only be prepared once the administration to the patient is confirmed (Merode *et al.* 2002, Vidal *et al.* 2010, Masselink *et al.* 2012). Advanced preparation of labels in the pharmacy (without preparing the actual drugs in advance) is also addressed (Lu *et al.* 2012).

Operational Planning

The main operational decision, patient-to-appointment assignment, can be divided in two stages: planning and scheduling, where planning is the selection of the day of treatment (Turkcan *et al.* 2012, Sevinc *et al.* 2013, Condotta and Shakhlevich 2014, Gocgun and Puterman 2014) and scheduling is the choice of the time of the day at which the treatment should start (Santibáñez *et al.* 2012, Turkcan *et al.* 2012, Sevinc *et al.* 2013, Condotta and Shakhlevich 2014, Hahn-Goldberg *et al.* 2014, Liang and Turkcan 2015, Liang *et al.* 2015). Nurse-patient assignment is another operational planning decision. It consists of the allocation of a group of patients to a nurse for a specific day - *functional care model* - or the assignment of patients to a nurse for the duration of their whole treatment - *primary care model* (Condotta and Shakhlevich 2014, Hahn-Goldberg *et al.* 2014, Liang and Turkcan 2015). Staff-shift assignment is also studied for nurse scheduling operations, i.e. defining when each nurse will work for a defined horizon (Woodall *et al.* 2013). In the pharmacy, the issue of scheduling drug preparation is the only operational planning aspect addressed (Mazier *et al.* 2010).

Table 2 Outpatient chemotherapy planning decisions

Decision/Issue	Definition	References
Patient planning	Select the date of the appointment	(Turkcan *et al.* 2012, Sadki *et al.* 2013, Sevinc *et al.* 2013, Condotta and Shakhlevich 2014, Gocgun and Puterman 2014)
Patient scheduling	Select the start time of the appointment	(Sepúlveda *et al.* 1999, Santibáñez *et al.* 2012, Turkcan *et al.* 2012, Yokouchi *et al.* 2012, Sevinc *et al.* 2013, Condotta and Shakhlevich 2014, Hahn-Goldberg *et al.* 2014, Huggins and Pérez 2014, Liang and Turkcan 2015, Liang *et al.* 2015)
Nurse scheduling	Define the working hours of nurses	(Woodall *et al.* 2013, Baril, Gascon, Miller, and Cote 2016)
Medical planning	Define the weekly consulting periods of oncologists for the next few months	(Sadki *et al.* 2013)
Resource allocation	Decide where to invest resources (nurses, chairs/beds, phlebotomists…)	(Baesler and Sepulveda 2001, Matta and Patterson 2007, Vanberkel *et al.* 2010, Lu *et al.* 2012)
Drug preparation scheduling	Define the pharmacy daily production schedule	(Merode *et al.* 2002, Mazier *et al.* 2010, Masselink *et al.* 2012)
Drug preparation policy	Define which drugs can be prepared in advance	(Mazier *et al.* 2010, Vidal *et al.* 2010, Masselink *et al.* 2012)

Nurse-patient assignment	Define the group of patients allotted to a nurse	(Santibáñez *et al.* 2012, Turkcan *et al.* 2012, Condotta and Shakhlevich 2014, Liang and Turkcan 2015)
Doctor-patient assignment	Define the group of patients allotted to a doctor	(Sadki *et al.* 2013)

4.3. KPIs for Outpatient Chemotherapy

The decisions as described in the previous section have an effect on the system performance measures. These are defined through different types of KPIs. The first category is resource-focused and is strongly related to costs. The second category consists of patient-centered metrics, i.e. KPIs that measure the patient path in the system. The third category deals with qualitative indicators, mainly satisfaction metrics. The fourth and last category focuses on the performance of drug preparation in the pharmacy.

Cost and Resource-Focused Metrics

A part of the KPIs in outpatient chemotherapy are similar to outpatient appointment scheduling (AS) performance measures. Cayirli and Veral (2003) define AS performance as a linear combination of the mean waiting time of patients, the mean idle time of doctors, the mean overtime of doctors and the associated cost parameters. These three aspects are also important for outpatient chemotherapy, where doctor overtime is used as a performance measure (Sadki *et al.* 2013). In the case of outpatient chemotherapy, nurses are also a crucial resource whilst they don’t intervene in outpatient consultation services. Therefore, authors studying outpatient chemotherapy planning account for nurses’ idle time (Turkcan *et al.* 2012) and overtime (van Lent *et al.* 2009, Turkcan *et al.* 2012, Liang and Turkcan 2015) in addition to that of doctors. Further metrics related to nurse scheduling and management are used. Existing studies employ indicators for nursing workload (Santibáñez *et al.* 2012) and workload excess measured in various ways (excess in patients over ideal practice (Santibáñez *et al.* 2012), sometimes analyzed as nurse overload (Liang and Turkcan 2015), nurse shortage (Woodall *et al.* 2013) or daily workload excess (Condotta and Shakhlevich 2014)). Some nurse planning studies use the number of clashes between nurses activities as an indicator to represent the number of occurrences when one nurse is planned for more than one activity at a given time (Condotta and Shakhlevich 2014) (e.g. nurse A should at the same time be setting up the drips of patients X and Y).

Some metrics mix staff categories, such as the number of patients per total staff or specific staff category (e.g. nurse) per unit of time (van Lent *et al.* 2009), or average staff occupancy (Baesler and Sepulveda 2001, Condotta and Shakhlevich 2014). Closing time, similarly to clinic overtime, is a common indicator (Sepúlveda *et al.* 1999, Baesler and Sepulveda 2001, Turkcan *et al.* 2012, Hahn-Goldberg *et al.* 2014, Liang *et al.* 2015), more rarely measured as the frequency of overtime (Matta and Patterson 2007) or the average number of chairs busy at the expected end of service (Sepúlveda *et al.* 1999).

In addition to staff, another important resource in outpatient chemotherapy clinics is chairs or beds. Indicators are thus used to measure the utilization of beds: number of patients per bed per unit of time (van Lent *et al.* 2009, Vanberkel *et al.* 2010), or the rate of bed occupancy (Vanberkel *et al.* 2010, Yokouchi *et al.* 2012, Sevinc *et al.* 2013, Liang *et al.* 2015), or the variation of the number of beds needed along the year (Sadki *et al.* 2013).

Finally, global measures assess the available capacity (Santibáñez *et al.* 2012, Huggins and Pérez 2014) and the number of patients per unit of time, also called throughput (Matta and Patterson 2007, van Lent *et al.* 2009). In the current patient-centered paradigm, KPIs are also defined to follow patient trajectories.

Patient-Centered Metrics

The first patient-centered metric is the patient waiting time, which can refer to two different delays. First, the time between the patient's call and her appointment (Santibáñez *et al.* 2012, Turkcan *et al.* 2012), sometimes referred to as the *appointment lead time* (Nguyen *et al.* 2015). When working on the appointment lead time, some authors use indicators of fairness for planning across different categories of patients (Condotta and Shakhlevich 2014), while others analyze the appointment notification lead time (Santibáñez *et al.* 2012). The waitlist size is also an indicator to evaluate the management of the appointment-making process (Santibáñez *et al.* 2012). The second type of patient waiting time is the delay on treatment day between the scheduled appointment and the actual beginning of the consultation or treatment (Sepúlveda *et al.* 1999, Baesler and Sepulveda 2001, Masselink *et al.* 2012, Santibáñez *et al.* 2012, Yokouchi *et al.* 2012, Woodall *et al.* 2013, Condotta and Shakhlevich 2014, Liang and Turkcan 2015, Liang *et al.* 2015, Baril, Gascon, Miller, and Cote 2016), referred to as *waiting time* (Nguyen *et al.* 2015). Waiting time is sometimes further divided between waiting time before consultation and waiting time before treatment (Liang *et al.* 2015). At the daily level, system time is a common measure of the time between arrival and departure of patients (Sepúlveda *et al.* 1999, Matta and Patterson 2007, Yokouchi *et al.* 2012, Huggins and Pérez 2014). The ratio of waiting time on system time is analyzed by Yokouchi et al. (2012). Matta and Patterson (2007) insist on differentiating temporal indicators between days of the week, patient classes and process steps.

In addition to these KPIs, outpatient chemotherapy management requires some specific indicators linked to its clinical specificity and recurring aspect. This is why Gocgun and Puterman (2014) measure the number of patients for which the strict treatment plan could not be followed. An example of this would be if a patient has a protocol with an injection on day 1 and another injection on day 8, but for some reason it is not possible to see her on day 8 and the injection happens on day 9. This impacts the dose intensity and can reduce treatment efficiency (Lyman 2009). In a similar way, Vanberkel et al. (2010) compute the number of patients that cannot be seen and must be rescheduled on the next day due to resource shortage.

Qualitative Indicators

Some qualitative indicators are also used. Patient satisfaction is not a typical indicator in OM/OR but it can be related to previously identified items, in particular waiting times. It is measured in some studies (van Lent *et al.* 2009, Santibáñez *et al.* 2012), sometimes as “number of complaints” (Baril, Gascon, Miller, and Cote 2016). Staff satisfaction is also analyzed (Santibáñez *et al.* 2012), as nurse turnover is an important concern in hospital management (O’Brien-Pallas *et al.* 2006, Hayes *et al.* 2012).

Pharmacy Indicators

The activity of drug preparation is fundamental for outpatient chemotherapy. It is measured through the workload (Santibáñez *et al.* 2012) or the number of preparations (Kergosien *et al.* 2011), and the productivity as the number of preparations per operator (Kergosien *et al.* 2011), and the staff utilization (Lu *et al.* 2012). Existing studies consider also temporal aspects, namely the pharmacy's delay to delivery (Kergosien *et al.* 2011, Lu *et al.* 2012), the rates of on-time and tardy jobs (Mazier *et al.* 2010, Kergosien *et al.* 2011), and the expected tardiness (Kergosien *et al.* 2011). Finally, drugs can be prepared in advance to avoid waiting times on the day of chemotherapy. If drugs are produced in advance (i.e. before the doctor has examined the patient and decided that she is in sufficiently good physical condition for treatment), there is a risk that the drug will be prepared but the patient will not be able to receive it. In such cases, the policy for advanced drug preparation is evaluated through the quantity and the cost of wasted drugs (Merode *et al.* 2002, Vidal *et al.* 2010, Masselink *et al.* 2012). Merode et al. (2002) propose also to evaluate the economic value of the drug inventory that is constituted by advanced preparation.

Now that outpatient chemotherapy has been presented from an organizational perspective, specificities on its modeling and analysis are next described.

5. Specific Complexities when Modeling Outpatient Chemotherapy Planning

Although outpatient chemotherapy planning shares some characteristics with other outpatient clinic planning issues, it has specificities which make it quite different to analyze and model. Three characteristics make it an original problem to study: coupled-operations issues, tolerances in planning and uncertainties on patient status. These three aspects have managerial and analytic implications that will now be detailed.

5.1. Coupled Operations Issues

Condotta and Shakhlevich (2014) show that the problem of outpatient chemotherapy planning lies in the category of scheduling coupled-operations jobs with exact time-lags. Coupled operations scheduling was first introduced for radar operations by Shapiro (1980). It is applied to cases when an operator or a machine has multiple tasks to perform on a product and these tasks need to be separated by a fixed time interval. When the resource is not working on one product because this job is in-between two tasks, it can work on another unit. This is typically the case for radars when they emit a signal, which then flows until it is reflected by a target, and comes back to the radar for reception. The radar is busy with this job during emission and reception but is available between these two tasks. From an algorithmic point-of-view, coupled operations scheduling on a single machine is NP-hard (Potts and Whitehead 2007).

In our case, coupled operations can be identified at two levels: for patient planning and for patient scheduling. For patient planning, i.e. determining the days of the appointments, multiple appointments are made for a patient with a specified delay between them. This is because chemotherapy works in cycles. Patient scheduling, i.e. determining appointment time once the date has been chosen, is another coupled-operation problem. On a treatment day, patients undergo multiple operations separated by a predefined duration. The nurse needs to be present to set up the infusion. She does not need to stay with the patient during the infusion, but she needs to come back at the end of the infusion. Patient scheduling is therefore a coupled operations problem.

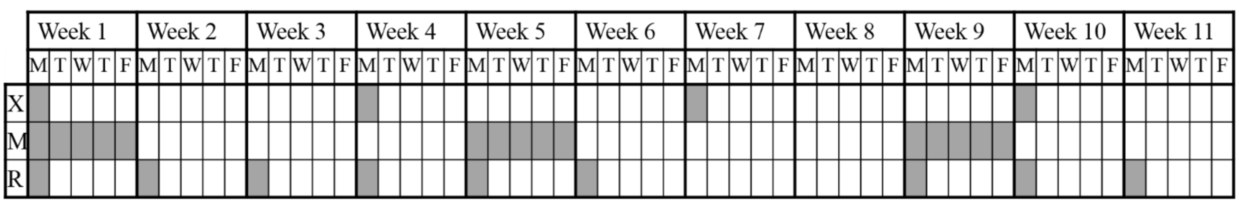

Fig. 2 11-week schedule for the Xelox (X), Mayo Clinic (M) and Roswell Park (R) regimens (only working days are indicated)

To clarify the chemotherapy specificity, an illustration is given next using the examples of the regimens presented in Section 3.1. In Figure 2, the three different regimens for colon cancer are shown as well as the appointments needed in these regimens over an 11-week horizon. For the Xelox regimen, the patient comes every 3 weeks for an injection and takes oral capacitabine for the first 14 days of the cycle. Therefore, the patient comes on day 1 of week 1, then on day 1 of week 4, day 1 of week 7, etc. The gray cases represent the days when the patient has to come to the hospital. Figure 3 shows what happens during the day for six patients followed by the same nurse. For the Xelox regimen, the patient comes for a 2-hour injection. It is assumed that the nurse needs 15 minutes to set the drip and 15 minutes to take it off. Between these two periods, the nurse is monitoring the drip but not actively involved in patient care. For the Mayo Clinic regimen, patients get a rapid infusion followed by a bolus (a quick subcutaneous injection). These patients only require two consecutive injections so they have a very short sojourn time at the clinic (15 minutes in Figure 3).

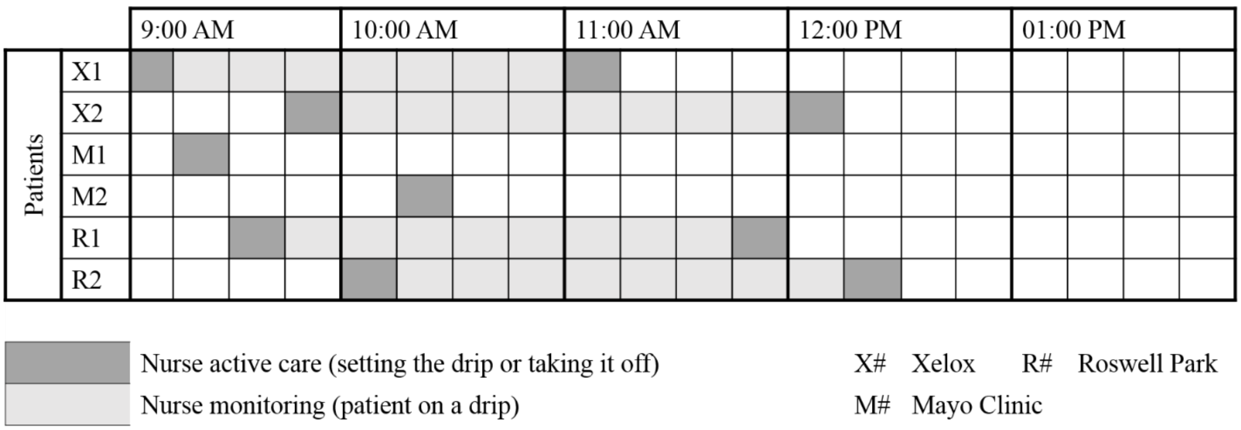

Fig. 3 Intra-day planning for six patients followed by the same nurse, with Xelox (X), Mayo Clinic (M) and Roswell Park (R) regimens (each hour is divided in 15-minutes period)

A nurse can manage a set of patients, depending on how much attention the patients do need, i.e. their "acuity levels" (Liang and Turkcan 2015). She can only "actively care" for one patient at a time. Thus there cannot be two cases with "nurse active care" in the same column in Figure 3. Higher acuity levels are required for example for a patient with respiratory assistance. Figure 3 shows only simple cases. It may be the case that a patient has to get a first infusion, then the drugs are changed for a second infusion, and only thereafter the patient is released. In such cases, the nurse is required to set up the infusion, then to change the infusion for the second drug mix, then to release the patient. This example illustrates that nurses can have more than two "active care" timeslots per patient.

Planning coupled events is different from planning single operations. To do so, various methods have been proposed. At the tactical level, medical planning (defining weekly consultation periods of oncologists for the next months) has been addressed by Sadki et al. (2013) using Mixed Integer Programming. The method consists of a three-stage approach to plan morning sessions first, then afternoon sessions, and finally improve solutions locally. At the operational level, patient planning has been modeled as a Multiple

Knapsack problem (Sevinc *et al.* 2013). For patient scheduling, multiobjective optimization can be used to identify tradeoffs between patient waiting-time, nurse overtime and nurse excess workload (Liang and Turkcan 2015). Constraint programming has also been used for dynamic patient scheduling, in an approach called dynamic template scheduling (Hahn-Goldberg *et al.* 2014). This approach can be extended to cover both patient planning and scheduling and is then called multilevel template scheduling (Condotta and Shakhlevich 2014). Finally, both planning and scheduling have been tackled with Mixed Integer Programming using heuristics for the numerical resolution (Turkcan *et al.* 2012).

5.2. Tolerances on Treatment Dates

Another distinctive characteristic of chemotherapy planning compared to other outpatient planning activities is the presence of due dates for appointments, and tolerances on the dates of appointments, which creates a time window for planning (Gocgun and Puterman 2014). Regimens must be followed strictly, e.g. when the second session must be planned 14 days after the first session, but they often include a tolerance margin of one or two days before or after the target date (Santibáñez *et al.* 2012). Tolerance values are set by oncologists when the regimen is created. It is acceptable to plan appointments in this tolerance zone as it is assumed that the dose intensity won't vary enough to decrease treatment efficiency. In practice, protocols with tolerances are common: in a study of a large cancer treatment center in Canada, more than 82% of the patients were following a protocol with a tolerance margin of plus-one or minus-one day (Santibáñez *et al.* 2012). Since they give more flexibility to planners, tolerances can be used to optimize scheduling and improve the efficiency of the clinic without compromising the efficacy of the treatments.

To take into account tolerances, Gocgun and Puterman (2014) develop a two-part cost function. The first part defines costs for scheduling outside the tolerance zone. The cost is zero when the appointment date is inside the tolerance zone. Outside the tolerance zone, the cost is proportional to the delay between the target date and the actual appointment. A first cost coefficient α is associated for planning too early and a second cost coefficient β for planning too late. Another part of the cost function is the cost of serving a patient through overtime inside his tolerance zone. If α and β have high values, planning outside tolerance zones has a higher cost and overtime will be preferred. In the reverse situation, the system will bend towards scheduling outside tolerances.

5.3. Uncertainty on Patient Status and Its Effect on Drug Preparation

No-shows are a typical issue in outpatient clinics (Muthuraman and Lawley 2008). A no-show is defined as a patient who does not show up at the time of her appointment. One of the main distinctive features of outpatient chemotherapy planning is that no-shows are quite rare. Instead, a patient who shows up can be actually not suitable for treatment. Based on the blood test or during the consultation, a patient can indeed be declared too weak for chemotherapy. At the Netherlands Cancer Institute, 10% of the patients whose blood is tested and 5% of the patients without blood tests are found to be unfit for treatment (Masselink *et al.* 2012). This is due to the disease itself, and to the side-effects of chemotherapy.

This feature has one important immediate consequence. With such rates of unfit patients, if all chemotherapies were prepared in advance the quantity of spoiled drugs would be huge. As some drugs cost up to thousands of dollars, this would be impossible. Therefore, pharmacies will be reluctant to prepare in advance without a guarantee that the patient will receive her treatment. A trade-off must be found between the risk of spoiling drugs and patient waiting time. In the literature, the Analytic Hierarchy Process has been used for this purpose (Vidal *et al.* 2010), as well as queueing theory (Masselink *et al.* 2012). Simulation can be employed to identify the effect of different policies (Merode *et al.* 2002).

To enable advanced preparation with a high level of certainty on the patient's status, some hospitals plan consultations on the day before chemotherapy (Dobish 2003). However, this solution drives patient transportation costs up and is not popular among patients (Lau *et al.* 2014). Other hospitals call patients one or two days before treatment to better anticipate their status (Coriat *et al.* 2012, Scotté *et al.* 2013). Patients often agree with such a procedure (McCann *et al.* 2009). A study by Scotté et al. (2013) reports that the percentage of drugs which were produced but could not be administered dropped from 6% to 2% of the total production due to a more reliable information on patients' physical status, and the patient waiting time was reduced by 66 minutes thanks to more preparations in advance. Another benefit in terms of the reduction of the number of unplanned hospitalization has been also underlined (Coriat *et al.* 2012).

6. The View from Practice: Outpatient Chemotherapy in a French Public General Hospital

Both managerial and analytical specificities of outpatient chemotherapy have now been presented. It is now interesting to understand and assess how well the existing literature addresses the important managerial challenges. In this section, we conduct a case study to investigate the theory-to-practice gap. The objective is to evidence, from practice, new opportunities for future research.

The case study is conducted in a French public university hospital near Paris. This is a large general hospital (1,000+ beds, 80,000+ inpatient admissions/year, and 300,000+ outpatient visits/year). The oncology department performs around 4,000 outpatient chemotherapy sessions per year. This number has been growing steadily in the past years: +20% between semester 1 of 2014 and semester 1 of 2015. One of the main issues of the management of the department is that patients are experiencing very long waiting times on the day of chemotherapy.

In the literature, most studies focus on cancer treatment centers or integrated cancer treatment clinics inside bigger hospitals (Sepúlveda *et al.* 1999, Baesler and Sepulveda 2001, Matta and Patterson 2007, Masselink *et al.* 2012, Woodall *et al.* 2013, Gocgun and Puterman 2014, Hahn-Goldberg *et al.* 2014, Huggins and Pérez 2014). Few papers study outpatient chemotherapy planning in general hospitals (Merode *et al.* 2002, Vidal *et al.* 2010, Lu *et al.* 2012, Yokouchi *et al.* 2012). Our analysis shows that outpatient chemotherapy planning for oncology departments in general hospitals differs on several points from what has been studied in the literature. The case study allows us to identify the related gaps between theory and practice.

6.1. Coordination with Actors outside the Hospital

In most articles on outpatient chemotherapy planning, blood tests are performed in the hospital, on the day of chemotherapy administration (Merode *et al.* 2002, Turkcan *et al.* 2012, Yokouchi *et al.* 2012, Woodall *et al.* 2013, Liang *et al.* 2015). In the studied hospital, blood tests are performed two days before chemotherapy delivery, in an external medical lab. This policy reduces waiting times and allows advanced drug preparation based on blood test results. It also saves capacity at the hospital's lab for inpatients and urgent cases. However, the hospital has no control over external labs. Therefore, coordination needs to be achieved between the oncology department and the external labs so that blood test results are transmitted on time. If the results are not transmitted on time, drug preparation cannot be started in advance. This is an additional source of uncertainty: the hospital depends on external actors. The situation is similar with respect to patient transportation. Patients handle on their own the transportation when they come to the hospital. However, for the return trip, it is often the nurse who calls the ambulance or the taxi. Patients regularly wait long times for their ambulance or taxi. This can be due to the transport supplier, or to nurses not calling soon enough.

6.2. Coordination between Hospital Departments

In the existing models centered on the pharmacy, it seems to be generally assumed that the pharmacy has only one client department requiring chemotherapy drugs (Mazier *et al.* 2010, Masselink *et al.* 2012). In our case, as shown in Figure 4, chemotherapy drugs are administered in different units: the oncology department, but also the hematology department, dermatology, etc. Outpatient oncology represents 37% of chemotherapy administrations, 26% for outpatient lymphoid hemopathies, and 11% for inpatient lymphoid hemopathies, followed by 10 % for inpatient clinical hematology. Overall, over 40 different units have ordered at least one chemotherapy preparation over an 18-month period. Even though the eight biggest client departments account for 90.6% of preparations, which makes the 30-odd others small variables, all these client departments are separate organizations with their own proper objectives, practices and clinical specificities. Scheduling in the pharmacy is complex: the pharmacy does not only need to satisfy the priorities of one department (the outpatient oncology department), it needs to juggle with different queues of orders. Fairness between departments is an additional constraint for the pharmacy. Moreover, actions taken to improve the situation locally, such as new patient planning rules in the oncology department for instance, will impact the workload of the pharmacy and may make the situation worse. The system is not only one where flows of drugs and patients have to be synchronized, it is also one where a single capacity must accommodate multiple heterogeneous clients.

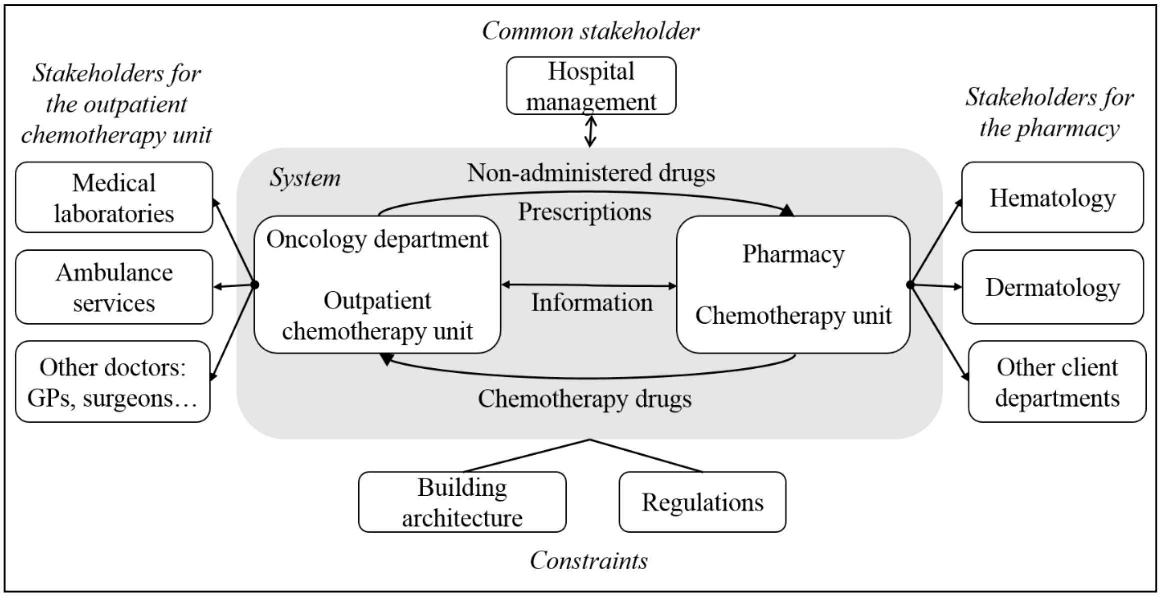

Fig. 4 Stakeholders for outpatient chemotherapy in the studied hospital

6.3. Drug Preparation Policy

Most papers assume that drugs are prepared on the day of chemotherapy delivery (Merode *et al.* 2002, Masselink *et al.* 2012, Turkcan *et al.* 2012, Yokouchi *et al.* 2012, Woodall *et al.* 2013, Huggins and Pérez 2014, Liang *et al.* 2015). One paper describes a case where part of the preparation (the administrative, office part) is done in advance (Lu *et al.* 2012). Only two papers (Vidal *et al.* 2010, Masselink *et al.* 2012) explicitly describe a mixed policy where part of the drugs are prepared before the patients see the oncologist and the rest is prepared after the medical examination. This is also the case in the studied hospital. Only for 16% of the preparations does the pharmacy wait for confirmation from the doctor (but these preparations account for 40% of the total value of preparations). For all other preparations, blood test results are transmitted before the patient's arrival to the hospital, and if they are positive, the preparation can start in advance. However, if the patient is ultimately not in shape for receiving chemotherapy, the drugs are then returned to the pharmacy. Returned drugs can be re-allocated during their stability period, but after that they must be destroyed, which is a net loss for the pharmacy. The value of all chemotherapy preparations is over 5 million euros per year: the trade-off in the drug preparation policy is crucial.

7. Discussion: Opportunities for Future Research

We have presented the organizational aspects of outpatient chemotherapy and the related challenges in terms of modeling and analysis. Based on the case study we carried in a French hospital, we discuss in this section the opportunities to reduce the theory-to-practice gap.

Most of the work published in the literature has focused on hospitals working as integrated care centers, rather than on “general hospitals”. In general hospitals, coordination issues are more challenging. One conclusion could be that all hospitals ought to change towards the integrated cancer center model. However, this is difficult, especially in less densely populated areas where hospitals face a lower number of patients with a wide range of pathologies. Therefore, in many hospitals, multiple departments will still have to collaborate to ensure good quality of care at high levels of efficiency. An efficient chemotherapy planning requires then an appropriate coordination between the involved subsystems: the lab for blood tests, the pharmacy for drug preparation and the outpatient clinics for drug administration. Different resources, with different skills, responsibilities, objectives and views on the performance of the system, need also to collaborate. This is a typical case where a focus on a subsystem’s performance can deteriorate the global system’s performance (Matta and Patterson 2007). New methods are thus required to tackle such challenging issues. In what follows, we distinguish the methods that could be used and we highlight that the link between patient waiting time, a common indicator and objective in the reviewed studies, and patient satisfaction needs to be studied further for outpatient chemotherapy.

7.1. Multiple Departments: the Challenge of Coordination

Although models of single departments "ignore the inherent complex interactions between decisions for different services in different organizations and departments" (Hulshof *et al.* 2012, p. 158), models with multiple departments are rare in healthcare (Vanberkel *et al.* 2009). Our case study shows that, in similar cases at least, the pharmacy, the outpatient clinic and the interaction between them should be modeled. In our review, except in two papers (Merode *et al.* 2002, Matta and Patterson 2007), the pharmacy is either the sole concern of the study (for studies of drug preparation scheduling) or considered as a simple step in chemotherapy administration. The reason could be that, in the integrated cancer centers studied in the literature, the pharmacy is a subunit of the outpatient department, or because drugs are prepared directly by nurses in the clinical department. In French hospitals, most pharmacies have been centralized to increase pharmaceutical control and traceability (Larrouturou *et al.* 1992, Favier *et al.* 1996, Cazin and Gosselin 1999, Martin *et al.* 2004). Similar recommendations have been issued in the United Kingdom (Turner *et al.* 2011) and Germany (Deutsche Gesellschaft für Onkologische Pharmazie 2009). The 2008 Quality Standard for the Oncology Pharmacy Service issued by the European Society of Oncology Pharmacy states that "the centralized preparation of CMR (carcinogenic, mutagenic and reprotoxic) drugs must take priority over distributed preparation" (German Society of Oncology Pharmacy 2008, p. 49). Therefore, our case study can be considered as representative of many European hospitals.

In France, the centralization of cytotoxic drug preparation allowed to buy appropriate equipment: isolators instead of vertical laminar air-flow hoods (Larrouturou *et al.* 1992, Cazin and Gosselin 1999). Isolators induce less risks of contamination and the centralized production allows cost savings (Favier *et al.* 1996). However, from a production angle, they are less flexible than a decentralized production with vertical laminar air-flow hoods: for instance, in the studied hospital, the machines have a 15 minutes sterilization phase before preparation and a 5 minutes sterilization phase after preparation, and they work in batches of four preparations. Single-piece flows are almost impossible. As a consequence of this centralization and operational structure, the pharmacy in the studied hospital is a separate department, with different objectives, which serves multiple departments. Reducing its complexity to a single stochastic variable, as is often the case in the literature, would be a risky simplification.

Various modeling techniques could be applied to multi-department issues. Mathematical programming and simulation, very popular in health care management science, can be developed in this direction. Moreover, to take into account the interests of multiple departments (pharmacy and outpatient departments), “softer” approaches including the interests of all stakeholders should also be investigated. In the papers reviewed here, only van Merode et al. (2002) mention the “political” dimension of re-organizations in multi-department systems. If these dimensions are not taken into account, “actors will try to fulfill their own particular interests” (Merode *et al.* 2002). Implementation of recommendations could then be jeopardized, which is a common issue in healthcare (Fone *et al.* 2003, Proudlove *et al.* 2006, Brailsford *et al.* 2009, Brailsford and Vissers 2011). In the case of simulation, projects using simulation “with a high level of implementation and user engagement in the simulation part” are very rare in healthcare compared to other sectors (Jahangirian *et al.* 2012). In the papers reviewed here, many use real data but only a limited number provide elements of implementation into regular practice – nine out of twenty-five (Mazier *et al.* 2010, Vidal *et al.* 2010, Lu *et al.* 2012, Masselink *et al.* 2012, Santibáñez *et al.* 2012, Sevinc *et al.* 2013, Woodall *et al.* 2013, Liang *et al.* 2015, Baril, Gascon, Miller, and Cote 2016) (the implementation of the results of Mazier et al. (2010) is presented in another paper by Kergosien et al. (2011)). This is still limited with regards to implementation. Soft OR methods could help here, as they have been developed to tackle human and political issues in order to overcome "the abstraction and impracticability of much OR/MS research" noticed in the late 1970’s (Mingers 2000). A way forward could be to combine Soft OR methods with traditional modeling and simulation techniques. This type of multimethodology has already been successfully applied in healthcare (Lehaney and Paul 1996, Kotiadis 2007, Holm *et al.* 2013). In the reviewed papers, Santibañez et al. (2012) have combined process observation and mapping with simulation. Another project in the Netherlands has combined qualitative (van Lent *et al.* 2009) and quantitative

(Masselink *et al.* 2012) approaches. A third paper in Canada combines simulation with Lean management and a business game (Baril, Gascon, Miller, and Cote 2016).

7.2. Patient Satisfaction and Waiting Times

Besides multi-department coordination, additional research should be undertaken on patient satisfaction predictors in outpatient chemotherapy. It is usually implicitly assumed that reducing patient waiting time is a priority, but evidence to back this objective is limited. Outpatient chemotherapy is different from emergency departments, where waiting time is a clinical variable. In outpatient chemotherapy, if decreasing waiting times has a limited impact on patient satisfaction, then actions should be undertaken to reduce it mainly for operational reasons (throughput, resource utilization) and the cost of actions to reduce waiting times should be evaluated precisely. The literature provides no definitive answer on the link between waiting times in chemotherapy and patient satisfaction. In the study of satisfaction factors in outpatient oncology care by Gesell and Gregory (2004), waiting time in the chemotherapy area is only the 10^{th} item whereas waiting time in the registration area is ranked 6^{th}. Actually waiting time is not a well-studied dimension of cancer patient satisfaction with the provided care (Sandoval *et al.* 2006). In a study by Sandoval et al. (2006), “Wait time from arrival to chemo treatment” and “Waited longer than expected for chemo treatment” are the areas with the highest problem frequency among the 1,044 Canadian chemotherapy patients who answered (66.7% and 70.4% respectively). However, they are not the best predictors for satisfaction and rank far behind management of confidential information and respect and communication aspects. In the literature review on the satisfaction determinants in cancer treatment by Lis et al. (2009), waiting times are regularly identified as dissatisfaction factors but only one study spots waiting time as a satisfaction predictor. In this study by Fossa et al. (1996), “Less than 1.5 hours at the out-patient department” is the highest predictor for patient satisfaction, so system time is important, but waiting time is not mentioned. System time depends on waiting time but also on treatment duration, which is a clinical variable, independent of the way operations are managed. More evidence needs to be gathered to understand the link between waiting time and patient satisfaction.

8. Conclusion

Although research on outpatient chemotherapy planning is rather young, it is quickly developing. Given the rising number of cancer cases, the ageing of the world population and the budget constraints, research on this topic should keep expanding. In this article, the literature is reviewed to identify the distinctive features of outpatient chemotherapy planning. Organizational aspects, with specific KPIs and inter-department structures, are evidenced. Modeling specificities are also underlined. By confronting the literature to the reality of a French public general hospital, some points are highlighted and should be kept in mind when tackling outpatient chemotherapy. One key point is to consider outpatient chemotherapy as a multiple department issue when drug preparation is centralized in the hospital. Future research should follow this systemic view rather than model the involved actors separately.

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