Incidence, Risk Factors and Treatment Outcomes of Extravasation of Cytotoxic Agents in an Outpatient Chemotherapy Clinic

Emiko Sakaida1, Ikuo Sekine1,*, Shunichiro Iwasawa1, Ryota Kurimoto1, Takashi Uehara2, Yoshihiko Ooka1, Naoki Akanuma1, Yuji Tada3, Chiaki Imai4, Tomoko Oku5 and Yuichi Takiguchi1

1Department of Medical Oncology, Graduate School of Medicine, Chiba University, Chiba, 2Department of Reproductive Medicine, Graduate School of Medicine, Chiba University, Chiba, 3Department of Respiratory Medicine, Graduate School of Medicine, Chiba University, Chiba, 4Division of Pharmacy, Chiba University Hospital, Chiba and 5Division of Nursing, Chiba University Hospital, Chiba, Japan

*For reprints and all correspondence: Ikuo Sekine, Department of Medical Oncology, Graduate School of Medicine, Chiba University, Inohana 1-8-1, Chuo-ku, Chiba 260-8670, Japan. E-mail: isekine@chiba-u.jp

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Objective: Extravasation, the accidental leakage of an anticancer agent from a vessel into the surrounding tissues, can lead to irreversible local injuries and severe disability. Despite its considerable clinical importance, evidence-based information on extravasation in chemotherapy is lacking. This study characterized the clinical features of extravasation and identified issues to be resolved in current cancer chemotherapy performed in outpatient settings.

Methods: We retrospectively reviewed the medical charts of patients who received chemotherapy and sustained extravasation in our Outpatient Chemotherapy Clinic from April 2007 to August 2012. Chemotherapy administration and extravasation management procedures were standardized using the in-house chemotherapy guideline.

Results: Among 43,557 patients who received chemotherapy, 35 (0.08%) experienced extravasation. The duration between the start of infusion and extravasation was >2 h in 28 (80.0%) patients. The severity of extravasation was Grades 1, 2 and 3 in 28, 2 and 5 patients, respectively—three of whom were associated with port trouble. The contributing factor for extravasation was walking in 11 (31.4%) patients. All extravasations were cured without surgical intervention by management according to our guidelines.

Conclusions: The incidence of extravasation is as low as 0.08%, using our in-house chemotherapy guideline. Extravasation from implanted ports tends to be severe.

Key words: chemotherapy — cytotoxic agents — extravasation — outpatient

INTRODUCTION

Systemic chemotherapy plays a pivotal role in curative therapy for patients with hematological neoplasms and several types of advanced solid tumors. Although several oral molecular-targeted agents have been developed recently, most anticancer agents are administered intravenously. Extravasation, the accidental leakage of an anticancer agent from a vessel into the surrounding tissues, is an unwanted and distressing complication that can lead to irreversible local injuries and severe disability (1). The incidence of extravasation in adults is estimated to be in the range from 0.01 to 6.9% (1), but few studies report the incidence on the basis of firm data with a total number of patients who received chemotherapy (2). The symptoms of extravasation can range from self-limited localized tissue inflammation to full-thickness necrosis, ulceration and sloughing of the skin and underlying structures. The extent of symptoms depends on the type of anticancer agent that seeps into the tissue, which can be categorized as vesicant, irritant or non-irritant (3).
In addition, the risk and severity of extravasation can be influenced by the infusion site, tissue condition, concentration and volume of the agent and treatment applied. Although these factors represent expert opinion, there are no data that are referred to while managing extravasation in anticancer agents.

Therefore, this study characterized the clinical features of extravasation and identified issues to be solved in current cancer chemotherapy performed in outpatient settings.

PATIENTS AND METHODS

All chemotherapy treatments for outpatients in the Chiba University Hospital have been integrated in the Outpatient Chemotherapy Clinic since 2007; patients referred by oncologists from the specialized outpatient clinics of this hospital are attended to between 9:00 and 17:00 h. Informed consent for chemotherapy is documented by an oncologist prior to chemotherapy. All chemotherapy regimens are submitted to and approved by the Institutional Chemotherapy Committee. A chemotherapy regimen is prescribed before the day of the chemotherapy, and pharmacists independently verify each order for chemotherapy before preparation. Principally, patients visit the Outpatient Chemotherapy Clinic before the day of chemotherapy, and an expert nurse explains chemotherapy in the clinic, especially calls patient’s attention to extravasation, the management of adverse events at home and the costs of chemotherapy. The agents are prepared by pharmacists in safety cabinets. Chemotherapy administration and extravasation management procedures are standardized according to the in-house chemotherapy guideline, which deals with duties and operations of stuffs, rules and engagements of the Outpatient Chemotherapy Clinic, safety management and the response to emergency. Peripheral veins are assessed carefully, and needle insertion into an antecubital vein is avoided if possible. Butterfly needles are not allowed. A transparent dressing is used to secure the insertion site. Vesicant agents are administered by drip infusion without any pump devices. A nurse visits patients for monitoring every 30 min and when a patient returns from the toilet, observes at the site of infusion and confirms a backflow of the blood, and records the findings on the check sheet. When an extravasation occurs or is suspected, the infusion is stopped immediately, and the affected area is inspected and aggregated weekly. For this study we retrospectively reviewed the extravasation sheet and medical charts of patients who sustained extravasation. The study was conducted in accordance with the ethical guideline for epidemiological research in Japan and was approved by the Chiba University Ethics Committee (no. 1702).

RESULTS

From April 2007 to August 2012, a total of 43 557 patients received chemotherapy in the Outpatient Chemotherapy Clinic. Of these, 35 (0.08%) patients experienced extravasation. The incidence decreased with each year: 0.11% in 2007 and 2008, 0.1% in 2009, 0.08 in 2010, 0.07 in 2011 and 0.01 in 2012. Sixteen patients complained of pain, burning sensation and/or discomfort at the site of infusion, which led to the detection of extravasation in these patients. An infusion pump alarm was another lead to find extravasation in three patients. In the remaining 16 patients, a nurse detected extravasation during her round of visits. Characteristics of these patients included 20 women and 15 men with a median age of 67 years (range, 37–80 years). Tumor types were eight breast cancers, seven colorectal cancers, six ovarian cancers, four lung cancers, two gastric cancers, two uterine cancers, two cholangiocarcinomas and four others. The blood access site was a peripheral vein in 29 (82.9%) patients (forearm in 18, cubital fossa in seven, dorsum of hand in two, upper arm in one and dorsum of foot in one patient), followed by a central venous port in four (11.4%) and arterial infusion port in two

The interval between the start of infusion and extravasation was >2 h in 28 (80.0%) patients. The median (range) number of chemotherapy administrations was 9 (1–70). Extravasated agents included vesicant in three patients (vinorelbine in two and vincristine in one patient), and irritant in 21 patients (paclitaxel in 12, docetaxel in 3, irinotecan in 3 and cyclophosphamide in 3 patients. In the three patients receiving a vesicant agent, the infusion site was the cubital fossa, forearm and dorsum of foot in one patient each. Extravasation was detected at the end of infusion in one and during infusion in two patients. No contributing factor was specified in these patients. The severity of extravasation was Grades 1, 2 and 3 in 28, 2 and 5 patients (three of whom were associated with port trouble), respectively (Table 1). The grades of extravasation of vesicant agents were Grades 1 and 2 in two and one patient, respectively. The contributing factor for extravasation was walking in 11 (31.4%) patients and not specified in 10 (28.6%) (Table 2). All extravasations were cured without surgical intervention as a result of management according to our guidelines.
DISCUSSION

Although extravasation in association with anticancer chemotherapy is well recognized, there are few reports on its incidence based on the exact number of patients. Langstein et al. (4) report 44 cases of extravasation among 240,000–360,000 individual doses of chemotherapy during a 6-year study period, suggesting the number of incidence to range from $\approx 0.012$ to 0.018%. In another report, 216 of 35,475 (0.61%) patients sustained extravasation (2). In contrast, small case series show that the incidence of extravasation is as high as 6% (5,6). This inconsistency among reports may be attributable to differences in the monitoring and notification systems for extravasation between hospitals. The incidence of extravasation in the present study among $\approx 44,000$ patients was 0.08% which is close to the lower limits of previous reports. The results of this study suggest our integrated multidisciplinary team in the Outpatient Chemotherapy Clinic has successfully standardized the procedure through chemotherapy preparation, administration and monitoring following our chemotherapy guideline.

In this study, extravasation was associated with a long infusion time of $>2$ h in 80% of cases. Furthermore, it occurred in one-third of patients just after walking to the toilet. This suggests that a small problem in the needle-insertion procedure exists. Thus, securing the needles and instructing patients not to move while an anticancer agent is being administered could be improved. Patient movement is a well-described risk factor for extravasation. The European Oncology Nursing Society extravasation guideline recommends that patients should be instructed not to leave the clinical area while a vesicant is being administered (7).

In the present study, only five patients sustained Grade 3 extravasation, and none required surgical intervention, mostly because there were only three vesicant extravasations. In addition, these were attributable to the early detection of extravasation, which led to only a small amount of anticancer agents leaking into the perivenous tissues. Since less than half of all patients complained of symptoms associated with extravasation, monitored by nurses is considered to have worked well. Among the three cases of vesicant extravasations, two and one were Grades 1 and 2, respectively, suggesting that our chemotherapy guideline and staff training work well and that the entire process from chemotherapy administration to the monitoring and management of extravasation is appropriate.

Although the exact incidence of extravasation associated with totally implantable venous access ports remains unknown, the risk of extravasation is believed to be lower when anticancer agents are infused through ports than temporary intravenous needles (8). In this study, three of four extravasations from implanted ports progressed to Grade 3 while the other progressed to Grade 1. This suggests that extravasation from implanted ports tends to cause severe tissue injury once it occurs. Because there are few specifically recommended procedures for the management of extravasation from
implanted ports, there is room for further development of specific guidelines on its management.

In conclusion, the incidence of extravasation among chemotherapy patients is as low as 0.08% with a well-trained multidisciplinary team using the in-house chemotherapy guideline in the Outpatient Chemotherapy Clinic. Extravasation from implanted ports tends to be severe and should be studied further.

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Conflict of interest statement

None declared.

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