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ORIGINAL ARTICLE

Improving Service Provision to Manage Chemotherapy-induced Neutropenic Fever in an Oncology Unit

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ABSTRACT

Objectives: *Neutropenic fever is a serious complication of cytotoxic chemotherapy with significant morbidity and mortality, for which prompt initiation of antibiotics improves clinical outcomes. International guidelines recommend a 'door-to-needle' time (DTN) for antibiotic administration within 2 hours as a performance standard in the management of neutropenic fever. This study set out to evaluate whether this target of DTN within 2 hours was being met in our institution. By identifying hurdles in the existing system, we anticipated deriving strategies to set up new workflow arrangements to improve our practice.*

Methods: *Two-stage retrospective audits were carried out. Oncology patients who were admitted for neutropenic fever after recent chemotherapy were identified from the hospital computer database. All paper and electronic medical records were reviewed and analysed to determine the DTN of antibiotic administration. System factors and attributes leading to major delays were identified along the patient care pathway. The result of the first audit was summarised, shared, and discussed among teams; strategies to overcome impediments were derived and implemented. A second audit using the same criteria was then carried out to evaluate the effectiveness of the changes.*

Results: *In the first phase of audit from 1 April 2011 to 30 November 2011, there were 32 patients. Overall, the median DTN was 261 minutes (range, 62-531 minutes); two patients (6%) achieved the 2-hour target. Patients admitted through the emergency department had a shorter median DTN than those admitted through the oncology clinic (222 vs 315 minutes). One patient (3%) died due to uncontrolled chest infection and cancer progression. Major attributes to prolonged DTNs were identified. They included (but were not limited to): a long waiting time for clinician assessment prior to hospital admission, and after being hospitalised, a long time interval between antibiotic prescription and administration. A list of actions to overcome these delays was proposed and worked out in departmental multidisciplinary meetings. At the same time, in the emergency department a clinical management protocol was set up and implemented to deal with patients having suspected neutropenic fever. After implementation of new workflows (both in the oncology and emergency departments), the second phase of audit was carried out from 1 April to 31 July 2012. This entailed 30 patients. Overall, there was a 64% reduction in the median DTN to 95 minutes (range, 25-231 minutes). The reduction in median DTN was noted in patients admitted via the emergency and oncology departments, being 79% (from 222 to 46 minutes) and 69% (from 315 to 98 minutes), respectively. Moreover, 63% (19/30) of the patients achieved the 2-hour target, which translated into a 11-fold improvement.*

Conclusion: *By modifying the existing system and workflows, clinical audits and collaborative multidisciplinary efforts significantly improved the service provided for the clinical management of patients with neutropenic fever.*

Key Words: *Antibiotic prophylaxis; Fever; Neutropenia; Quality improvement; Time factors*

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中文摘要

腫瘤科中化療致中性粒細胞減少性發熱患者的改善治療

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目的：中性粒細胞減少性發熱是細胞毒性化療的一種嚴重併發症，發病率和死亡率都相當高，迅速啟動抗生素治療可改善臨床結果。國際指南推薦中性粒細胞減少性發熱治療的「就診—用藥」時間（DTN）標準為不超過兩小時，即從病人到醫院至給予抗生素治療的時間應在兩個小時內。本研究評估我們的機構是否達到DTN在兩小時內的目標。通過識別現有工作系統的制約因素，我們期望制定策略以設立新的工作流程來改善臨床治療。

方法：本研究分為兩個回顧性審計階段。從醫院電子數據庫中篩選出化療後因中性粒細胞減少性發熱入院的腫瘤患者，回顧所有紙質和電子病歷並進行分析，以確定施予抗生素的DTN。沿病人護理流程找出系統因素和引致重大延誤的因素。組間總結、分享和討論首次審計結果，制定策略克服制約因素的策略並實施。然後根據相同的標準進行第二次審計以評估新工作流程的成效。

結果：2011年4月1日至11月30日期間進行的第一階段審計中，共有32名患者。總體而言，DTN的中位數為261分鐘（介乎62至531分鐘）；其中2例（6%）達兩小時的目標。與腫瘤診所的患者比較，通過急診室入院的患者有較短的DTN中位數（222比315分鐘）。1例（3%）因胸部感染無法控制和癌症惡化而死亡。廷長了DTN的因素包括（但不僅限於）：入院前等待臨床醫生評估的時間太長，以及入院後抗生素處方發出到給藥的間隔時間太長。跨學科醫務人員會議提議並制定出克服延誤的一系列措施。與此同時，急症室亦制定並實施新的臨床管理方案以處理中性粒細胞減少性發熱的疑似病例。在腫瘤科和急症室內實施了新的工作流程後，於2012年4月1日至7月31日期間進行第二階段的審計，共有30名患者。總體而言，DTN中位數減少至95分鐘（介乎25至231分鐘），減幅達64%。在腫瘤科和急症室的DTN中位數均有減少：急症室減幅達79%（從222分鐘減至46分鐘）；腫瘤科減幅達69%（從315分鐘減至98分鐘）。此外，63%（19/30）的患者達到了兩小時內的目標，即有11倍的改善。

結論：經臨床審核及多個學科醫務人員的協作努力，現有工作系統和工作流程得以修改，從而使中性粒細胞減少性發熱患者的臨床診療服務顯著改善。

INTRODUCTION

Neutropenia is a well-known side-effect of cytotoxic chemotherapy.[1] The severity and duration of neutropenia correlates with the risk of infection and death.[2] All patients with neutropenia are at risk of developing neutropenic fever, which is always regarded as an oncological emergency because of its potentially fatal outcome. About 20 to 30% neutropenic fever patients have established bacteraemia. The overall mortality of neutropenic fever ranges from 5 to 20%, with the highest mortality rate in those with Gram-negative bacteraemia.[3] Moreover, it is also associated with significant morbidity and hospitalisation costs.[4] Prompt administration of antibiotics has proven benefits in terms of survival in patients with severe sepsis or septic shock. A study in 2010 showed a significant association between in-hospital mortality and time from triage in the emergency department (ED) to appropriate antibiotics using a 1-hour cut-off time (the mortality rate being 19.5% vs 33.2%; odds ratio = 0.30; p = 0.02).[5]

With the increasing use of chemotherapy, we are expecting to see more and more patients developing adverse events from such treatments. In 2008, a review conducted in the United Kingdom[6] showed that only 35% patients who had developed complications after chemotherapy were judged to receive satisfactory care, while in 38% a scope for improvement in clinical care was recognised. Among these, the management of neutropenic fever was identified as one of the key areas that were unsatisfactorily.[6] In response, in 2009 the National Chemotherapy Advisory Group published

a guideline, which recommends each hospital has clear policies on the management of neutropenic fever.[7] It also urged ensuring rapid delivery of antibiotics for patients presented with neutropenic sepsis (within 1 hour).[7] In the United States, the 2010 updated guidelines on the management of neutropenic patients from the Infectious Disease Society of America also recommended initiating treatment with broad-spectrum empirical antibiotics promptly, i.e. within 2 hours of presentation.[8]

To address this issue, several reviews from different institutes have been performed to evaluate performance and identify potential areas for improvement. A 2003 United States study found the mean time to antibiotic administration was around 2 hours and 30 minutes.[9] More recently, a national audit from United Kingdom reported the median 'door-to-needle' time (DTN) ranged from 30 minutes to 4 hours for haemato-oncology patients presenting with neutropenic fever, with only 26% receiving antibiotics within the target of 1 hour.[10] In Canada, a similar audit showed that the median time from triage to antibiotic administration was 5 hours.[11]

This audit was undertaken in an oncology unit in Hong Kong. The objectives of our audit were to (1) evaluate whether the target DTN was met, and (2) identify potential barriers to achieving the target and make recommendations to overcome those that were identified.

Definitions and Audit Standard

Neutropenic fever was defined as an oral temperature equal to or higher than 38°C for at least 1 hour or one reading of ≥38.3°C, and associated with an absolute neutrophil count of less than 0.5 x 10^9 /L, or a count of less than 1 x 10^9 /L with a predicted decrease to below 0.5 x 10^9 /L.[9]

Patients with solid tumours presenting with or suspected to have neutropenic fever were admitted to the oncology ward via either the ED or oncology Specialist Outpatient Clinic (SOPC). Based on our local protocol, all suspected neutropenic fever cases were advised to have hospitalised care with reverse isolation facilities. Broad-spectrum antibiotics (piperacillin-tazobactam, cefoperazone-sulbactam, or a combination of piperacillin and amikacin) were initiated as a stat treatment followed by regular doses.

The DTN of antibiotic administration was defined as the time interval between arrival to ED or SOPC and the time of administration of the first dose of broad-spectrum antibiotics. According to our local policy, the audit standard for DTN was set at ≤2 hours.

For the purpose of subsequent data analysis, the DTN was further broken down into several critical periods along the patient care pathway (Figure 1), as follows:

(1) Door-to-ward time (DTW): the time interval

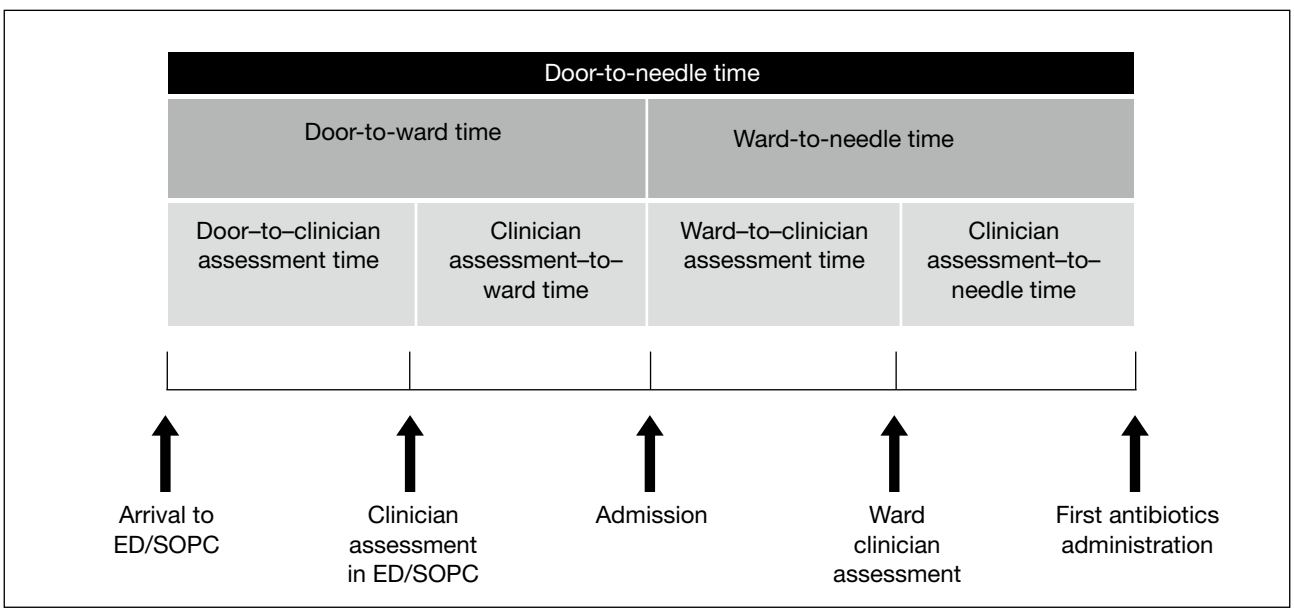

Figure 1. Patient care pathway for neutropenic fever.
Abbreviations: ED = emergency department; SOPC = Specialist Outpatient Clinic.

between arrival to ED or SOPC and the time of admission to the oncology ward, which was further subdivided into:

a) Door–to–clinician assessment time (DTC): the time interval between arrival to ED or SOPC and the time of clinician assessment in the ED or SOPC; and
b) Clinician assessment–to–ward time: the time interval between the clinical assessment in the ED or SOPC and the time of admission (arrival) in the oncology ward.

(2) Ward-to-needle time (WTN): the time interval between patient's arrival to oncology ward and the time of administration of the first dose of antibiotics, which was further subdivided into:

a) Ward–to–clinician assessment time (WTC): the time interval between admission to ward and the time of assessment by ward clinicians; and
b) Clinician assessment–to–needle time (CTN): the time interval between ward clinician assessment and the time of administration of first dose of antibiotics.

METHODS

Hospital discharge records with ICD9 diagnosis code of 288.0 ("neutropenic fever") were retrieved from hospital computer database. A single auditor, who was a higher clinical oncology specialty trainee, was responsible to carry out all the document reviews to ensure consistency. Clinical oncology specialist input was sought if there was controversy or ambiguity. Patients were included if they had solid cancers and admitted for management of confirmed or suspected neutropenic fever after recent use (within the prior 3 weeks) of cytotoxic chemotherapy. Patients who developed neutropenic fever during their hospital stay were excluded because it was difficult to determine a meaningful 'door' time.

All paper and electronic medical records were retrospectively reviewed to determine all the critical time points as defined above. The DTN and other time intervals were then determined. Other demographics and treatment data were also captured during the reviews.

After the first-phase audit, major attributes prolonging the DTN were identified. The results of the first audit were shared within the department. A multidisciplinary meeting was called to derive strategies to improve performance. After implementation of changes, a second phase of audit using the same methods was repeated to determine the effectiveness of the changes.

Statistical Analysis

Chi-square test was used to compare differences in gender, sites of primary malignancies, and treatment outcome based on modifications in chemotherapy cycles between patients included in first and second phase of the audit. The Mann-Whitney test was used to compare the median age, median DTN, median DTC, and median CTN. For all tests, a $p < 0.05$ was considered statistically significant.

RESULTS

Demographic Details

The first phase of the audit was carried out from 1 April 2011 to 30 November 2011, and involved 32 patients (group A). After implementation of changes, the second phase of audit was performed from 1 April 2012 to 31 July 2012, and involved 30 patients (group B). Patient demographics and chemotherapy details are shown in Tables 1 and 2. Breast cancer patients on adjuvant chemotherapy constituted the majority of the neutropenic fever admissions.

Seven (22%) patients in group A and one (3%) in group B had sources of infection identified (Table 3). The choices of broad-spectrum antibiotics and the use of granulocyte colony–stimulating factors are shown in Table 4.

Results of the First Audit

Door-to-needle Time

The median DTN was 261 minutes with a wide range that spanned from 62 minutes to 531 minutes. The median DTN was shorter for patients presenting via the ED than the SOPC (222 minutes vs 315 minutes). Only 6% (2 out of 32) of the patients received

Table 1. Patient demographics.

Demographics	No. (%) of patients		p Value
	Group A (n = 32)	Group B (n = 30)	
Median (range) age (years)	58 (22-71)	56 (30-76)	0.50
Sex			0.59
Female	30 (94%)	27 (90%)	
Male	2 (6%)	3 (10%)	
Site of primary malignancies			0.37
Breast	20 (63%)	26 (87%)	
Colorectal	4 (13%)	2 (7%)	
Lung	3 (9%)	1 (3%)	
Ovary	3 (9%)	1 (3%)	
Cervix	1 (3%)	-	
Pancreas	1 (3%)	-	

Table 2. Details of chemotherapy treatments.

Treatment	No. (%) of patients	
	Group A (n = 32)	Group B (n = 30)
Intent of chemotherapy		
Adjuvant	21 (66%)	26 (87%)
Palliative	9 (28%)	4 (13%)
Radical	2 (6%)	-
Chemotherapy regimens		
FEC	9 (28%)	15 (50%)
AC	2 (6%)	4 (13%)
Taxotere	8 (25%)	1 (3%)
TT/C	1 (3%)	5 (17%)
TAC	1 (3%)	-
Xeliri	3 (10%)	2 (7%)
EP/EC	3 (10%)	1 (3%)
TC	2 (6%)	2 (7%)
Caelyx	1 (3%)	-
Gem/Tar	1 (3%)	-
5FU (chemoRT)	1 (3%)	-

Abbreviations: FEC = 5-fluorouracil, epirubicin, cyclophosphamide; AC = doxorubicin, cyclophosphamide; TT/C = docetaxel, cyclophosphamide; TAC = docetaxel, doxorubicin, cyclophosphamide; Xeliri = capecitabine, irinotecan; EP = etoposide, cisplatin; EC = etoposide, carboplatin; TC = paclitaxel, carboplatin; Gem/Tar = gemcitabine, erlotinib; 5FU = 5-fluorouracil; chemoRT = concurrent chemoirradiation.

Table 3. Identified sources of infection.

Source	No. (%) of patients	
	Group A (n = 32)	Group B (n = 30)
None	25 (78%)	29 (97%)
Blood	4 (13%)	1 (3%)*
Chest	2 (6%)	1 (3%)*
Urine	1 (3%)	0

* Same patient.

Table 4. Use of antibiotics and growth factor.

Antibiotics / growth factor	Group A (n = 32)	Group B (n = 30)
Antibiotics used		
Piperacillin / Tazobactam	24 (75%)	4 (13%)
Piperacillin	3 (10%)	0
Cefoperazone / Sulbactam	2 (6%)	23 (77%)
Augmentin	2 (6%)	1 (3%)
Combination	1 (3%)*	2 (7%)†
Stat dose of antibiotics		
No	18 (56%)	5 (17%)
Yes	14 (44%)	25 (83%)
Use of G-CSF during hospitalisation		
No	28 (88%)	27 (90%)
Yes	4 (12%)	3 (10%)

Abbreviation: G-CSF = granulocyte colony–stimulating factors.
* Piperacillin and amikacin.
† Augmentin and ciprofloxacin.

antibiotics within the 2-hour target, both of whom were admitted via the ED. The longest DTNs for ED and SOPC patients were 531 minutes and 430 minutes, respectively.

Disregarding the route of admission, the median WTN constituted more than half the median DTN (Figure 2).

Door-to-ward Time

The overall median DTW was 77 minutes (range, 15-254 minutes; Figure 2). For both ED and SOPC, nearly

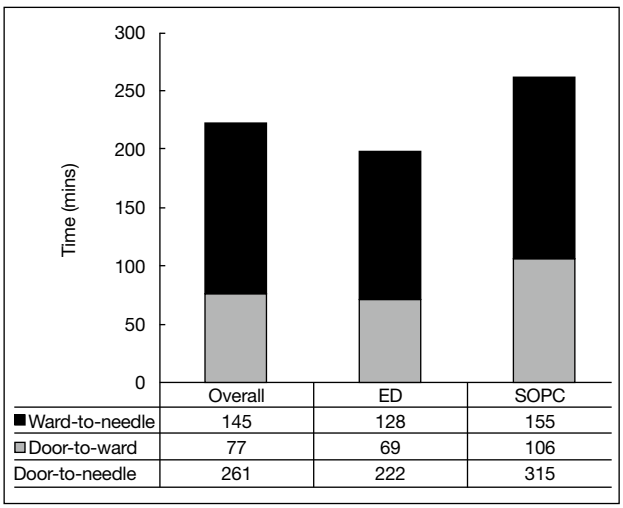

Figure 2. Median door-to-needle time in group A: subdivided into ward-to-needle time and door-to-ward time in all cases, in emergency department (ED) cases and specialist outpatient clinic (SOPC) cases.

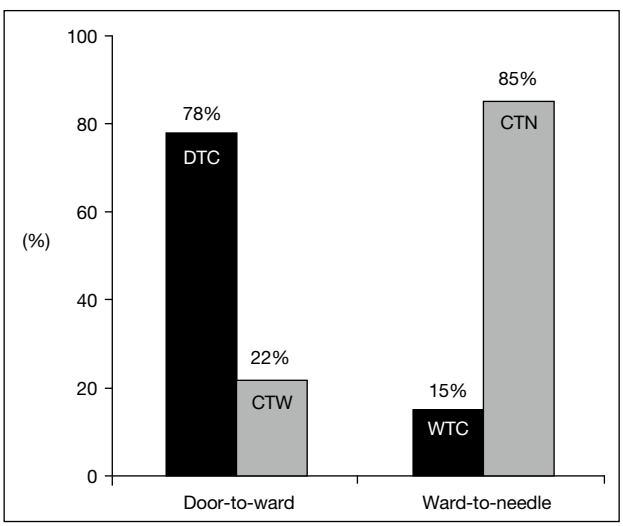

Figure 3. Components of different time intervals in door-to-ward time and ward-to-needle time by proportions in group A.
Abbreviations: CTW = clinician assessment–to–ward time; CTN = clinician assessment–to–needle time; DTC = door–to–clinician assessment time; WTC = ward–to–clinician assessment time.

Table 5. Reasons for delay in 'door-to-needle' time and strategies for improvement.

Problems identified	Strategies for improvement
Lack of awareness of typical presentation of neutropenic fever, potential risk, and the importance of early antibiotic administration	Education to medical and nursing staff about the importance of prompt administration of antibiotics. Introduce the current worldwide standard and the concept of 'door-to-needle time'
Lack of a triage system to identify the patients presented to specialist outpatient clinic	Set up a triage system with standard criteria to identify the potential case of neutropenic fever
Late turn-around time of the full blood count result	Empirical antibiotics would be initiated before laboratory result available
Long waiting time for phlebotomist to set up the intravenous line	Intravenous access would be set up by doctors during blood culture sampling
First antibiotics dose was administered on next drug round instead of urgent treatment	Enforce the practice of prescribing stat dose of antibiotics followed by regular doses
Prescription was not handled immediately by nurse	A consensus was made on the target action time of less than 30 minutes (from prescription and drug administration was set)
Long turn-around time from vetting of the prescription by pharmacist to drug dispensing	Pharmacists have agreed to vet the prescription on urgent basis; a limited stock of antibiotics for urgent use is available in oncology ward

80% of the DTW was attributable to the DTC (median, 62 minutes; Figure 3). On average, patients need to wait longer in SOPC than in the ED (median values being 91 vs 54 minutes).

Ward-to-needle Time

The overall median WTN time was 145 minutes (range, 6-355 minutes; Figure 2). The long WTN was mainly due to the long interval between ward clinician assessments to antibiotics injection (CTN) [Figure 3]. The WTC and CTN medians were 22 and 118 minutes, respectively.

Reasons for Door-to-needle Time Delays and Recommendations for Improvement

Based on the result of the first audit, we noted that the major contributors for delayed DTNs were (1) delay before admission owing to long DTCs, and (2) after admission, prolonged CTNs. The wide ranges of these time intervals indicated a lack of unified standards and practices within our service, leading to wide variations in performance.

The results of the first audit were summarised and shared in departmental multidisciplinary meetings. Major hurdles in the system contributing to delays were identified and listed. Improved strategies were jointly promulgated by the multidisciplinary team and implemented (Table 5). At the same time, a new management protocol for neutropenic fever patients was developed and implemented in the ED, following a collaborative effort by the emergency physicians, oncologists, haematologists, microbiologists, and clinical pharmacists.

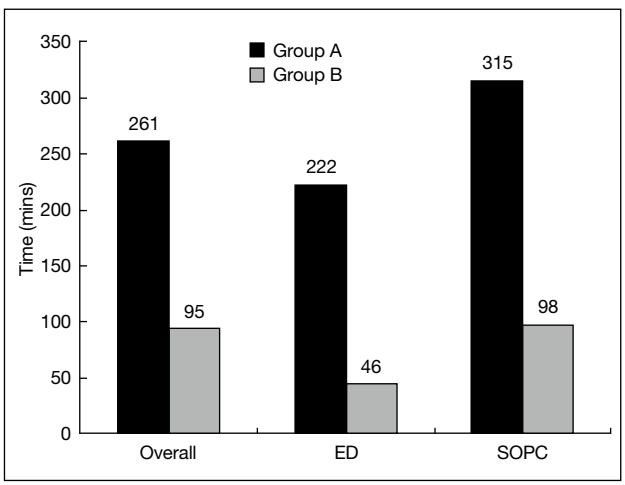

Figure 4. Median 'door-to-needle' time in groups A and B ($p < 0.0001$ for all).
Abbreviations: ED = emergency department; SOPC = Specialist Outpatient Clinic.

Results after Implementation of Changes (Second Audit)

Compared to the first audit, in the second audit the median DTN was reduced by 64% to 95 minutes (range, 25-231 minutes; $p < 0.0001$). Improvements were noted in patients admitted via both the ED and the SOPC (Figure 4). Moreover, 63% (19/30) of the patients achieved the target DTN of 2 hours, which translates into 11-fold improvement.

The shortening of DTN was mainly due to reductions in both the DTCs (before admission) and the CTNs (after admission). Overall, the median DTC was reduced by 65% to 22 minutes. Both ED and SOPC admissions

achieved similar DTCs (Figure 5a). The median CTN was reduced by 79% to 25 minutes (Figure 5b).

Treatment Outcomes

The treatment outcomes of groups A and B were comparable in terms of median durations of hospital stays (5 days vs 4 days) and modifications in subsequent chemotherapy cycles (dose reduction in 56% vs 60%; use of prophylactic growth factor in 6% vs 13%; both dose reduction and use of growth factor ensued in 13%). In group A, three patients (9%) had stopped chemotherapy prematurely. One patient (3%) in each group died, both due to documented chest infections (Table 6).

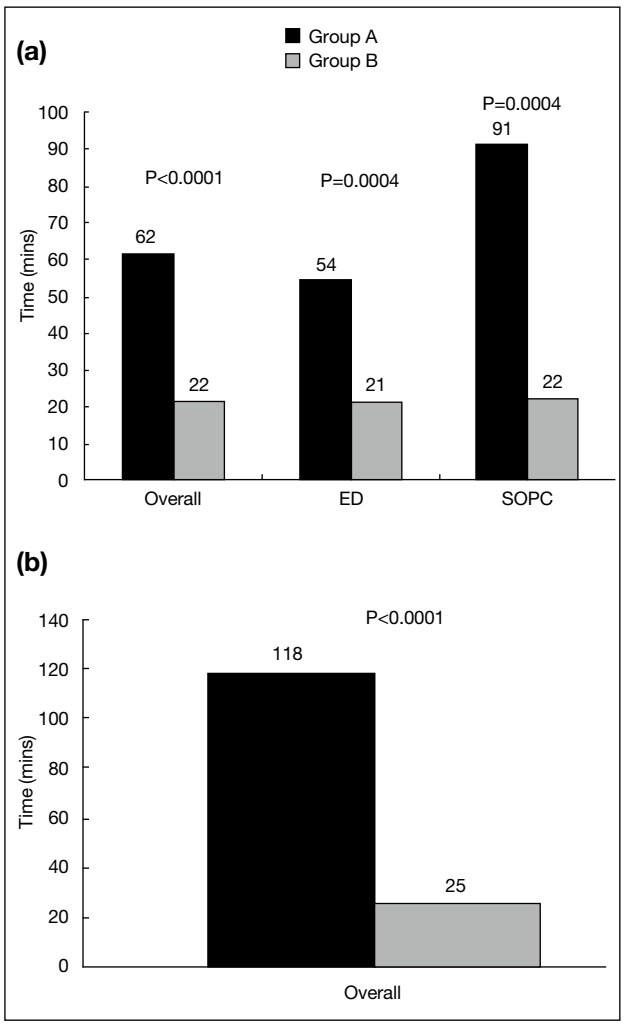

Figure 5. (a) Median door-to-clinician assessment time in groups A and B, and (b) overall clinician assessment-to-needle time.

DISCUSSION

The major difference between a clinical trial and an audit is the question they pose. In the former, we are asking "are we doing the right things?", whilst in the latter we are asking "are we doing the things right?". The results of a well-conducted clinical trial shed light to provide us with an evidence-based foundation on how we should manage our patients. Whereas the results of a clinical audit help us to know how we are performing what we know to be right. Thus, if outcomes turn out to be far from perfect in terms of what is anticipated, we can determine where and what should be improved.

Neutropenic fever is a well-known potentially fatal complication of cytotoxic chemotherapy. The management principles of neutropenic sepsis are basically no different from other serious septic conditions. Just as in other severe septic conditions that implies timely initiation of appropriate antimicrobial therapy to achieve maximal clinical benefit. With the increasing use of chemotherapy, especially in radical and adjuvant settings, it is also important for the oncology professionals to be aware of the particular risks and associated complications of the treatment that they offer. As a matter of fact, many of the international authorities have proposed to incorporating a DTN of within 1 to 2 hour as the performance measure in the management of neutropenic fever.[8,9] Following these international guidelines, audits and reviews have been performed in different parts of the world to evaluate

Table 6. Treatment outcomes.

Treatment outcome	No. (%) of patients		p Value
	Group A (n = 32)	Group B (n = 30)	
Median (range) length of hospital stays (days)	5 (2-19)	4 (2-9)	
Modifications in subsequent chemotherapy cycles			0.604
Dose reduction	19 (60%)	18 (60%)	
Use of prophylactic growth factor	2 (6%)	4 (14%)	
Dose reduction and use of growth factor	4 (13%)	4 (14%)	
Premature stop of chemotherapy	3 (9%)	0	
No alternation	2 (6%)	2 (7%)	
Unknown	1 (3%)	1 (3%)	
Mortality	1 (3%)	1 (3%)	

prevailing practices. Most of these reviews have shown that major delays in antibiotics treatment are quite common.[9-12] Disappointingly, this was also the case in our institution.

Nevertheless, with data from the first audit we could understand more about the weaknesses and deficiencies of what we were doing, and could introduce strategies and actions to remove obstacles to better patient care. During the first phase of audit, the two major 'bottlenecks' that hindered the speed of patient care were the long waiting time for doctors' initial assessments in the ED or SOPC, and the long action time for antibiotic administration after doctors had written the prescription. As mentioned before, the reasons for such delays are multifactorial (Table 5). Through the collaborative work of different disciplines (doctors, nurses, clinical pharmacist, and clerical staff), we could identify major obstacles within the existing system. Then we devised ways to remove them one-by-one. In particular, we found that setting up clear performance targets, good communication channels, and a robust triage system for frontline staff were keys to success. Other important initiatives included streamlining prescription and drug-dispensing logistics.

We are glad to report that the changes that we made impacted our performance favourably, as reflected by the second audit. However, there is still room for further improvement. During the second phase of audit, the DTNs in SOPC patients were still longer than those for ED patients, despite both groups having similar waiting times for initial doctor consultations (DTC) and similar time for antibiotic administration after the prescription (CTN). We found that for neutropenic fever patients admitted from SOPC, extra time was spent in ward admission procedures as well as ward physician assessments. Whereas for patients that attended the ED with neutropenic fever, antibiotics were administered immediately (before admission to the oncology ward). To further shorten the DTN especially for those attending the SOPCs, the feasibility of keeping a stock of antibiotics in the clinic for urgent use should be explored.

One limitation of our audits was that we could not show any tangible impact on the final outcomes of patients after improving DTNs. This could be due to the small number of patients and their very small overall mortality. However, addressing this question was not the primary purpose of these clinical audits. A second limitation was that our audit did not evaluate the potential impact of any delays in presentation to the hospital.

CONCLUSIONS

By modifying the existing system and workflows, clinical audits and collaborative multidisciplinary efforts can significantly improve service provision for the clinical management of patients with neutropenic fever. Setting up clear performance targets, good communication channels, and a robust triage system for frontline staff are the keys to success.

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