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Comparative Diagnostic Performance of the Granulocyte and Neutrophil Counts

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ABSTRACT

Objectives: Use of point-of-care testing is increasing, however many haematology analysers can only determine granulocyte count without further differentiation into neutrophils, eosinophils and basophils. Since the diagnosis of life-threatening neutropenia in cancer patients requires a distinct neutrophil count, this study aimed to determine the comparative performance between the neutrophil and granulocyte count.

Design and methods: A database of 508 646 venous full blood count results measured on a laboratory reference analyser was mined from a large oncology unit. The relationship between granulocyte and neutrophil counts was assessed. Multinomial logistic regression was used to classify results into neutropenia grades using an equivalent granulocyte count.

Results: Granulocyte to neutrophil count correlation was 0.997. The accuracy for classification into neutropenia grades using the derived equivalent granulocyte count ranges was 96.4%. Identification of results with a neutrophil count $< 1.5 \times 10^9$ cells/L using an equivalent granulocyte count of $< 1.69 \times 10^9$ cells/L resulted in sensitivity, specificity, positive and negative predictive values of 98.0%, 99.5%, 97.8% and 99.5%, respectively.

Conclusions: These results describe the relationship between granulocyte and neutrophil counts, measured on a laboratory analyser, in a large population of patients with malignancies and receiving anti-cancer therapies. However, this relationship must be established using a point of care testing system with a three-part differential count before considering the possibility that a granulocyte count can guide clinical decisions in the absence of a definitive neutrophil count, to reduce the frequency and severity of neutropenic complications in patients receiving cancer treatments.

1. Introduction

The technology of morphological assessment and counting of blood cells has advanced over recent decades, particularly in the

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white cell lineage, with concomitant benefits in relation to diagnosis, prognosis and management of inflammatory and malignant conditions. The full range of measurements is available on modern automated laboratory analysers. However, dependence on a service provided by a central laboratory has certain limitations, with potential clinical, operational and economic implications. These issues could arise in any setting where rapid decision making is required, e.g. the Emergency Department, primary care, a paramedical rural service, an out-of-hours doctor service or in the home, as well as in middle- and low-income countries [1–5].

One of the major technological advances has been in the recognition and quantification of differential white count. The initial three-part differential count expanded to the five-part differential count, with differentiation of the granulocyte count into neutrophil, basophil and eosinophil counts. Viral and bacterial infections are arguably the most common cause of acquired neutropenia [6,7], through margination of neutrophils and destruction by circulating antibodies [8]. Neutrophil levels may also be decreased due to congenital haematological malignancies [9], as a result of radiotherapy [10] or through the use of cytotoxic chemotherapy drugs [11]. Extreme reductions in neutrophil count can lead to serious complications such as febrile neutropenia (fever $> 38^{\circ}C$ and neutrophil count $< 0.5 \times 10^9$cells/L [12]), increasing the risk of sepsis-associated mortality [13], necessitating urgent clinical assessment in at risk patients. Thus, most chemotherapy patients are given immediate empirical antibiotics upon suspicion of infection [14]. In such patients, access to a rapid differential white count is vital as delays in administration of broad-spectrum intravenous antibiotics are associated with increased mortality risk, but overtreatment with unnecessary antibiotics has opportunity costs [15].

Access to the absolute neutrophil count (ANC) can be difficult in the early phase of developing neutropenia in patients on chemotherapy. These patients tend to be at home, and a health-care professional is required to obtain a venous sample from frequently accessed veins which need to be preserved for delivery of chemotherapy, but are often already compromised by vesicant and irritant cytotoxic drugs. Thus, it is not routine practice to monitor the neutrophil count during the chemotherapy cycle unless the patient reports symptoms suggestive of developing severe neutropenia complicated by infection.

There have been very few studies comparing the diagnostic performance of granulocyte and neutrophil counts in patients receiving chemotherapy. The aims of this study were to (i) determine the threshold of total granulocytes which represents a neutrophil count which signals a change in patient management, and (ii) determine if total granulocytes could be used as a meaningful indicator of neutrophil count in the neutropenic range for cancer patients receiving chemotherapy. This study was the first step in determining whether it was valid to consider the use of a granulocyte count for monitoring patients receiving chemotherapy.

2. Material and methods

2.1. Study design and patient selection

Analysis was conducted on a pseudonymised, retrospective database containing peripheral venous blood sample results between 1 January 2004 and 1 September 2013 from 21,020 patients, all of whom had received chemotherapy treatment at the Leeds Cancer Centre, Leeds Teaching Hospitals Trust (LTHT). The LTHT results server receives blood test results from the pathology laboratories and displays them in the electronic patient recording system (Patient Pathway Manager (PPM)) [16,17]. A pseudonymised extract was taken and inserted into a research database. No identifiable data was contained within the dataset and the research was sanctioned under the information governance procedures of LTHT, with data extraction pseudonymisation procedures as agreed with the Caldicott Guardian and with formal approval from a national research ethics committee (NHS Grampian ID: 13/NS/0128). No patients were excluded based on their chemotherapy treatment, demographic information, diagnosis or timing of treatment.

Blood counts were measured from EDTA venous whole blood samples obtained for the purposes of routine clinical care, and taken at any time in relation to chemotherapy delivery. All samples were submitted for a full blood count analysis, including a five-part differential on a Siemens ADVIA 120 analyser (Siemens Healthcare Diagnostics, Erlangen, Germany) until August 2004 and subsequently on the Siemens ADVIA 2120 analyser; both instruments employ the same method principles. All instruments were subjected to multiple quality control (QC) checks each day according to standard laboratory protocols, and the laboratory participated in the United Kingdom National External Quality Assessment Service (UKNEQAS) external quality assurance scheme.

Data of interest included the eosinophil, basophil and neutrophil counts, with the sum of these three parameters being taken as the granulocyte count (calculated in Microsoft SQL Server). Lymphocyte and monocyte results were also extracted for analysis. As within-day timing information was not available, if a patient had more than one blood test on a given day all data for that day was excluded to avoid ambiguity as to which result should be taken as the true value for that day.

2.2. Correlation and regression analysis

The R programming language package was used to conduct all statistical analysis and produce all figures [18]. Pearson's product-moment correlations were used to measure the strength of the linear association between complete granulocyte count and each of its components (eosinophils, basophils and neutrophils); $p < 0.05$ was considered significant. To correct for the differences in scale, raw count data was log transformed and standardized ($x' = [\ln \{x\} - \text{mean}(\ln \{x\})] / \text{standard deviation}(\ln\{x\})$. Passing-Bablok regression analysis was conducted using the MCR package for R [19]. This was performed separately on subsets of individuals with neutrophil counts classified as N0-N1 (normal to grade 1 neutropenia, ≥ 1.5 to $\leq 7.5 \times 10^9$ cells/L) and N2-N4 (grade 2–4 neutropenia, $< 1.5 \times 10^9$ cells/L) using grading criteria defined by The Common Terminology Criteria for Adverse Events [20]. To limit the memory requirements and computational overhead, the regression analysis was on a random subset of 32,000 results in each subset.