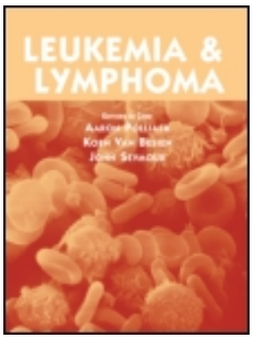

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Andrew Artz & David Pitrak

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COMMENTARY

Separating correlation from prediction: C-reactive protein and infectious complications after chemotherapy for acute myeloid leukemia

ANDREW ARTZ[1] & DAVID PITRAK[2]

[1]*Section of Hematology/Oncology, and* [2]*Section of Infectious Diseases, Department of Medicine, University of Chicago Chicago, IL, USA*

Infectious complications remain the major cause of acute morbidity and mortality during remission induction chemotherapy for acute leukemia. In this issue, Hämäläinen and colleagues explored the epidemiology of neutropenic fever after chemotherapy for adult acute myeloid leukemia (AML) [1]. The investigators further ascertained the value of serial C-reactive protein (CRP) levels to predict serious infectious complications.

They analyzed 84 adults treated for AML with a median age of 50 years (range, 18–69 years) resulting in 290 neutropenic episodes. Induction remission generally employed continuous infusion of cytosine arabinoside and idarubucin, then a second induction using the same drugs but cytosine arabinoside at higher dose, followed by consolidation chemotherapy. CRP was measured three times a week or more often when fever occurred.

Neutropenic fever occurred in 97% of all neutropenic episodes with bacteremia documented in 59% of febrile occurrences. After the first induction therapy, ten patients (13%) developed sepsis, seven (8%) required intensive care unit (ICU) admission and four patients (5%) died. Across all episodes of neutropenic fever, nine patients (11%) died from infection. The high rate of infectious complications is expected for AML patients undergoing induction therapy. Atallah and colleagues reviewed the MD Anderson Cancer Center experience of 1500 AML patients undergoing intensive chemotherapy and found fever in 94%, ICU admission in 28% and 16% six week overall mortality (for all causes) [2]. The higher rate of adverse outcomes in the MD Anderson series reflects the fact that almost 50% of the patients were 60 years or older compared to a median age of 50 years in the present report by Hämäläinen.

An increasing body of literature has shown that antibiotic prophylaxis can reduce bacteremia and possibly improve survival for leukemia patients undergoing chemotherapy treatment [3]. In this series, where antibiotic prophylaxis was not used, the occurrence of bacteremia in over 50% of episodes offers a historical control that further justifies antibiotic prophylaxis. However, routine prophylaxis and broad-spectrum anti-infective treatment may promote bacterial antibiotic resistance and lead to toxicities. Thus, risk-adapted approaches enabling early recognition of patients likely to suffer serious infectious morbidity would be invaluable. A rapid test that could identify patients at risk for severe sepsis and death would assure appropriate initial broad anti-infective therapy and/or ICU admission, interventions that could avert catastrophic complications. Further, lower risk patients could be considered for more narrow-spectrum anti-infective therapy, thereby minimizing antibiotic resistance and toxicities.

Serum inflammatory biomarkers such as (CRP) is one strategy that has been tested to better risk-stratify for severe infection. The most innovative aspect of this report was the serial evaluation of CRP and temporal correlation to infectious outcomes. Other investigators have previously shown that a greater rise in CRP among patients having neutropenic fever correlates with infection [4]. Further, a lesser rise in CRP and other inflammatory markers during neutropenic fever correlates with a reduced chance of bacteremia [5,6]. Inflammatory markers have not gained widespread acceptance in this setting because the added clinical value is unknown. Hämäläinen and investigators help provide clarity. Consistent with prior data, a greater rise in CRP two to three days after fever ($P < 0.001$) and higher peak CRP

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($P < 0.001$) correlated with sepsis. However, the rise in CRP coincided, rather then preceded, clinical changes of sepsis. Moreover, CRP values at the time of fever but before sepsis did not predict the outcome. The authors conclude that rises in CRP do not reliably predict serious infectious complications before clinical deterioration related to a limited window period; sepsis developed at a median of two days from the onset of neutropenic fever. Thus, while CRP changes correlate with infectious complications, the correlation has no defined role to predict clinically useful outcomes and allow changes in management strategies.

The authors should be lauded for their detailed investigation of infectious complications, meticulous correlation of CRP to clinical changes and for an honest assessment of relevance. This ''negative'' result is quite useful and should guide future studies. Other approaches that may be fruitful include using a panel of inflammatory markers [6] or more frequent biomarker assessment (e.g., every day or every 12 hours). However any new test must add to clinically available information such as hypotension, hypoxia, high fever or overt infection (e.g., pneumonia). Clearly, early recognition of serious infectious complications after acute leukemia intensive therapy remains a high priority.

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