


# Supportive care in the management of patients with acute myeloid leukaemia: where are the research needs?

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Supportive care for patients with acute myeloid leukaemia (AML) is defined as a broad range of interventions that ameliorate the symptoms of a disease, or the side effects caused by treatment, and which address psychological, cultural, social and spiritual factors.<sup>1</sup> Transfusion support and infection management are key examples of supportive care that have contributed significantly to the successes of more intensive chemotherapy, delivering improvements in outcomes despite, arguably, only modest improvements in chemotherapy regimens.<sup>2</sup> This article will review our current practice of transfusion therapy and infection management and identify research opportunities which the National Cancer Research Institute (NCRI) AML working party are supporting, alongside forthcoming national AML trials.

## The role of transfusion in patients in AML

There are many more randomised trials comparing different policies for platelet transfusion than red cell transfusion in patients with haematological malignancies. More recent randomised trials of platelet transfusion, including studies enrolling AML patients, have compared prophylactic versus non-prophylactic transfusion regimens. These prophylaxis trials established a small benefit for platelet transfusions in the reduction of bleeding, but with varied response between patient subgroups. Crucially, no reduction in *clinical* bleeding was seen in patients receiving autologous stem cell transplant (SCT), and significant bleeding still occurred in patients, *despite* receiving prophylactic platelet infusion.<sup>3,4</sup> A number of trials are now exploring the effectiveness of tranexamic acid as an adjunct (TREATT; NCT03136445, NCT02578901) or alternative to platelet transfusions (PATH; NCT02650791).

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The small number of randomised trials comparing different red cell transfusion policies in patients with haematological malignancies, including AML, is surprising, given that many thousands of patients have been enrolled into red cell transfusion trials in other settings.<sup>5,6</sup> The National Institute for Health and Care Excellence recommend a red cell threshold of 70 g/l for non-bleeding patients who are not chronically transfused and do not have a current diagnosis of acute coronary syndrome.<sup>7</sup> A recent study recruiting 300 patients undergoing SCT, reported that a restrictive red blood cell transfusion strategy (threshold of 70 g/l) was as effective as a threshold of 90 g/l for a primary outcome of health related quality of life (Tay et al., 2016). In the UK, a recent trial confirmed the feasibility of comparing a 70–90 g/l red cell transfusion threshold in patients with AML undergoing intensive chemotherapy (BSH abstract 2020), while an earlier feasibility study comparing a threshold of 70 *versus* 80 g/l in acute leukaemia patients was also successful.<sup>8</sup> No definitive study in AML has been completed. Therapeutic management of patients with AML is increasingly moving into outpatient settings. As such, it is of interest that in patients with myelodysplasia a recent trial comparing a restrictive transfusion threshold (80 g/l) with a liberal threshold (105 g/l) suggested a potential improvement in quality of life in patients managed on the liberal arm.<sup>9</sup> However, all transfusions are biological products carrying risks. The toxic oxygen-radical inducing non-transferrin bound iron (NTBI) has long been shown to be increased in the context of bone marrow failure or chemotherapy.<sup>10</sup> Clinically relevant consequences of this rise in NTBI include a higher rate of infection.<sup>11</sup> An exploratory study showed apotransferrin reduced NTBI in this group of patients,<sup>12</sup> but further studies are required.

## How can we reduce the severity of infections in patients with AML?

Infection remains a major cause of morbidity and mortality in AML. In one international study, nearly a third of patients

who developed neutropenia secondary to intensive chemotherapy developed invasive infections during their first neutropenic episode and the Hazard Ratio (HR) for death during invasive infection was 5.8 (95% CI: 2.5–13.0).<sup>13</sup> Despite this, haematologists recognise that whilst some patients develop severe or frequent infections, a proportion develop milder infectious complications, but the reasons for this variation are unclear.

Multiple strategies for infection management have been trialled but these tend to be characterised by non-targeted prophylaxis and empirical changes in antimicrobials in the face of fever. There have been important studies of prophylactic antibiotics and antifungals, although improvements in mortality are not consistently demonstrated<sup>14</sup> and have to be set against a backdrop of increasing antibiotic resistance globally, reducing the desirability and efficacy of such interventions.

As well as improving our understanding of pathogen profiles and pharmacological interventions to better manage infection, interventions that support patient and carer empowerment, such as dietary interventions, may have a role. The role of nutrients in the development and function of immune cells is well described.<sup>15</sup> Neutropenic diets remain commonplace, despite evidence of their efficacy being equivocal<sup>16</sup> and highly restrictive practices may compound nutrient deficiencies. Infective risk in cancer patients during intensive chemotherapy has been associated with malnutrition<sup>17</sup> and poor glycaemic control.<sup>18</sup> Knowledge of supportive nutritional interventions, such as immunonutrition and dietary manipulation to support microbiota diversity, is evolving rapidly.<sup>19</sup>

Novel high throughput techniques are now being applied to enable investigators to document changes in the immune system and microbiome. A recent study has shown change in microbiome diversity is predictive of outcome post allogeneic SCT.<sup>20</sup> Ultimately, one aim would be to identify biomarkers of infection risk to accurately predict incipient infection.

## Conclusion

A key consideration for both transfusion and infection management is how best to deliver individualised care. Current strategies for transfusion tend to be based on numbers (e.g. platelet count) while antimicrobial therapy is prescribed according to universal algorithms. There is a need to develop better, risk-stratified ways of using (or avoiding) both blood components and antimicrobials that reflect an individual patient's risk. It is imperative that patient and public involvement in research (PPI) groups<sup>21</sup> are involved in the development of supportive care trials from the choice of intervention, to the outcomes upon which it will be measured. These supportive care questions are important to patients and clinicians, but demand the highest quality evidence through prospective, randomised controlled trials to confirm (or refute) hypotheses and understand associated risks.

## Acknowledgements

Members of NCRI AML Supportive Care/ Transfusion Working Party: Dr Harpreet Kaur (Sheffield), Dr Priyanka Mehta (Bristol), Dr Victoria Potter (London), Dr Neil McCarthy (London), Prof Philip Calder (Southampton), and Dr David Partridge (Sheffield). We wish to acknowledge valuable input from patient and public involvement (PPI) members (Jane Leahy, Gill Murphy, Richard Castle, Joanna Calder and colleagues) and discussions with the NCRI AML working party, including Paresh Vyas (Oxford), Steve Knapper (Cardiff) and Charles Craddock (Birmingham).

## Author contributions

All authors were involved in the writing of the paper. All authors read and approved the final manuscript.

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