bjh short report

Stable long-term risk of leukaemia in patients with severe congenital neutropenia maintained on G-CSF therapy

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Summary

In severe congenital neutropenia (SCN), long-term therapy with granulocyte colony-stimulating factor (G-CSF) has reduced mortality from sepsis, revealing an underlying predisposition to myelodysplastic syndrome and acute myeloid leukaemia (MDS/AML). We have reported the early pattern of evolution to MDS/AML, but the long-term risk remains uncertain. We updated a prospective study of 374 SCN patients on long-term G-CSF enrolled in the Severe Chronic Neutropenia International Registry. Long-term, the annual risk of MDS/AML attained a plateau (2·3%/year after 10 years). This risk now appears similar to, rather than higher than, the risk of AML in Fanconi anaemia and dyskeratosis congenita.

Keywords: severe congenital neutropenia, acute myeloid leukaemia, myelodysplastic syndromes, granulocyte colony-stimulating factor.

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Severe congenital neutropenia (SCN) is a genetically heterogeneous disorder of myelopoeisis that is diagnosed clinically on the basis of an absolute neutrophil count (ANC) persistently below the threshold of $0{\cdot}5 \times 10^9$/l, with maturation arrest of neutrophil precursors in the bone marrow (Ancliff, 2003). Maintenance therapy with granulocyte colony-stimulating factor (G-CSF) is standard of care to prevent life-threatening bacterial sepsis (Dale *et al*, 1993). The success of G-CSF in averting mortality from sepsis (sepsis deaths) has unmasked a notable predisposition to myelodysplastic

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syndrome and acute myeloid leukaemia (MDS/AML) (Freedman *et al*, 2000). This susceptibility appears greatest in patients who require higher doses of G-CSF to achieve an adequate neutrophil response (Rosenberg *et al*, 2006).

We previously characterized the natural history of SCN patients maintained on G-CSF, using prospective observational study of 374 patients enrolled in the Severe Chronic Neutropenia International Registry (SCNIR) (Rosenberg *et al*, 2006). At the time of that report, long-term follow-up was limited, but available data suggested that the risk of MDS/AML in SCN rose to extraordinary levels, perhaps 8%/year after 12 years on G-CSF, albeit with a substantial margin for error. The apparent increase in the hazard curve for MDS/AML has been a cause for concern among patients and their physicians, and raised therapeutic and aetiological questions (Dale & Link, 2009). Hence, obtaining a more precise characterization of the risk profile is of considerable clinical and scientific importance. To this end, we updated the prospective follow-up data of the same cohort to obtain more accurate estimates.

Patients, materials and methods

The Severe Chronic Neutropenia International Registry

We updated prospective follow-up data of 374 well-characterized SCN patients on long-term G-CSF enrolled in the SCNIR. We ascertained event-free time, sepsis deaths, and MDS/AML events that accrued since our previous report, which ended 26 February 2001, through to 10 July 2009. For purposes of this analysis, follow-up was censored at the time of bone marrow transplant. Data on baseline G-CSF dose at month 6 of treatment was abstracted from registry and medical records, and converted to units of micrograms per kilogram per day (μg/kg per d), as described previously (Rosenberg *et al*, 2006). Data on mean ANC counts (cells $\times 10^9$/l) during months 6–18 on treatment were also abstracted. The study was conducted in accordance with the Declaration of Helsinki under the auspices of the Human Subjects Committee of the University of Washington and other participating institutions. Patients provided informed consent.

Statistical methods

SCN patients are at risk of both MDS/AML and sepsis death, which we analysed as competing adverse events. The time scale was years on G-CSF therapy. We obtained flexible and smooth estimates of the cause-specific hazards of MDS/AML and sepsis death using spline functions (Rosenberg, 1995). The cumulative incidence of each adverse event was estimated using the nonparametric maximum likelihood estimator (Gaynor *et al*, 1993). The effects of baseline G-CSF dose on the hazard of each adverse event were estimated using Cox proportional hazards models applied to follow-up from month 6 onwards. All statistical tests were two-sided. *P* values ≤ 0·05 were considered statistically significant.

Results and discussion

The update yielded a total of 3590 person-years of follow-up, *versus* 2043 in the prior report (Rosenberg *et al*, 2006). Follow-up was censored in 19 patients who received a bone marrow transplant. There were 849 person-years among 176 patients treated for 10 or more years; *versus* just 67 person-years among 60 patients previously. In all, there were 61 MDS/AML events and 29 sepsis deaths, *versus* prior totals of 44 and 19, respectively. After including up-to-date follow-up, the estimated annual hazard of sepsis death remained qualitatively stable, at 0·81%/year [95% confidence interval (CI): 0·56 – 1·16%/year]. Similarly, during the first 5 years after the start of G-CSF therapy, the updated estimate of the hazard curve for MDS/AML showed the same increasing trend as the previous estimate (Fig 1A). However, in contrast to the prior estimate

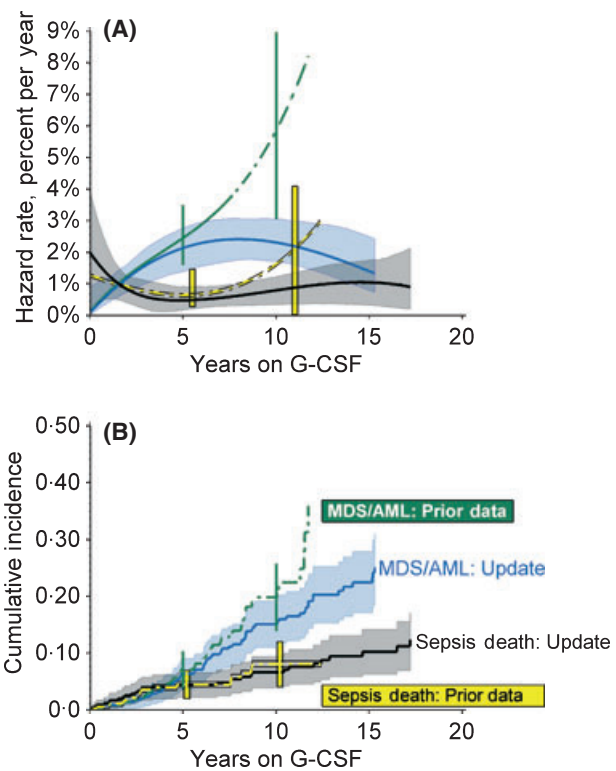

Fig 1. Hazard rates and cumulative incidence of MDS/AML and sepsis death in patients with SCN. (A) Annual hazard rates (incidence rate per year among patients who are still susceptible) for MDS/AML and sepsis death, by years on therapy with G-CSF. Dot-dash curves (green for MDS/AML and yellow for sepsis death) show estimates obtained from prior data (Rosenberg *et al*, 2006); solid curves (blue for MDS/AML and grey for sepsis death) show estimates obtained using updated follow-up. Shaded regions show point-wise 95% confidence envelopes for new estimates; error bars show point-wise 95% confidence intervals for previous estimates at selected years. (B) Corresponding estimates of cumulative incidence (cumulative proportion experiencing each event as initial cause of failure, in patients at risk of each adverse event), by years on G-CSF therapy, using updated follow-up (solid curves and shaded regions), compared with prior data (dot-dash curves and error bars).

that showed an increasing trend after year 5 (with a large margin for error), the updated hazard curve attained a plateau, with confidence intervals for the new hazard curve considerably narrower than corresponding intervals in our earlier report (Rosenberg *et al*, 2006). After 10 years on G-CSF, the estimated hazard of MDS/AML was 2·3%/year (95% CI: 1·7–2·9%/year).

Whereas the long-term hazard of MDS/AML now appears significantly lower than first suggested, substantial numbers of sepsis deaths and cases of MDS/AML accumulated over time. After 15 years on G-CSF, the cumulative incidence was 10% (95% CI: 6–14%) for sepsis death and 22% (95% CI: 17–28%) for MDS/AML Fig 1B). In the initial dataset, the corresponding estimates of cumulative incidence attained similar values earlier, 8% and 21% at 10 years, respectively.

With additional follow-up, the association of G-CSF dose at 6 months with the relative hazard of MDS/AML became more strongly statistically significant [$P = 0{\cdot}003$ vs. $P = 0{\cdot}024$; the hazard of MDS/AML increased by 1·24-fold (95% CI: 1·08-1·43-fold) per doubling of the G-CSF dose]. In contrast, the association of G-CSF dose at 6 months with the relative hazard of sepsis death was slightly attenuated [$P = 0{\cdot}053$ vs. $P = 0{\cdot}039$; the hazard of sepsis death increased by 1·25-fold (95% CI: 1·00 – 1·56-fold) per doubling].

As in the previous analysis, the subset of patients who failed to achieve a mean ANC count at or above the median for the cohort ($2{\cdot}188 \times 10^9$/l) despite doses of G-CSF at or above the median (8 μg/kg per d), were at elevated risk of both sepsis death and MDS/AML, compared with patients who achieved a good response at a lower dose (i.e. median ANC count above $2{\cdot}188 \times 10^9$/l on G-CSF below 8 μg/kg per d). In the low-risk group, the cumulative incidence after 15 years on G-CSF was 5% (95% CI: 0–12%) for sepsis death and 15% (95% CI: 4–25%) for MDS/AML (Fig 2A), *versus* 18% (95% CI: 7–28%) and 34% (95% CI: 21–47%), respectively, in the high-risk group (Fig 2B).

This analysis incorporates extended follow-up of the largest existing cohort of patients with SCN, which has allowed us to estimate the long-term risks with greater precision. Overall, comparisons of the new results (2009) with the old (2001) are very consistent. However, there is one important exception: in all patients combined, the hazard of MDS/AML now appears to be around 2·3%/year after 10 years on G-CSF, substantially below the range of 4–12%/year suggested by prior unstable data.

This is good news for patients and their physicians. Also, the reduced hazard estimate for MDS/AML helps resolve an aetiological conundrum. From a molecular perspective, it was not entirely clear why susceptibility to leukaemia appeared higher in SCN than in other high-risk inherited bone marrow failure syndromes, including the DNA repair disorder of Fanconi anaemia (FA) (Rosenberg *et al*, 2003) or the telomere maintenance syndrome of dyskeratosis congenita (DC) (Alter *et al*, 2009). Indeed, the high incidence of leukaemic transformation in SCN had raised concerns that G-CSF may promote malignant clones (Donadieu *et al*, 2005). In light of these new data, it now appears that the rate of MDS/AML in SCN is qualitatively quite similar to the rate of AML in both FA and DC. Furthermore, a plateau is now seen in SCN, similar to that for FA.

The positive news in this report must be put in perspective. Although the hazard curve for MDS/AML in SCN now appears to plateau, the cumulative incidence still attains high levels, albeit more slowly. Hence, it is imperative that all patients continue to be closely monitored for leukaemic transformation. Furthermore, the risks and benefits of early haematopoietic stem cell transplantation should be evaluated for the subset of patients who respond poorly to a high dose of G-CSF.

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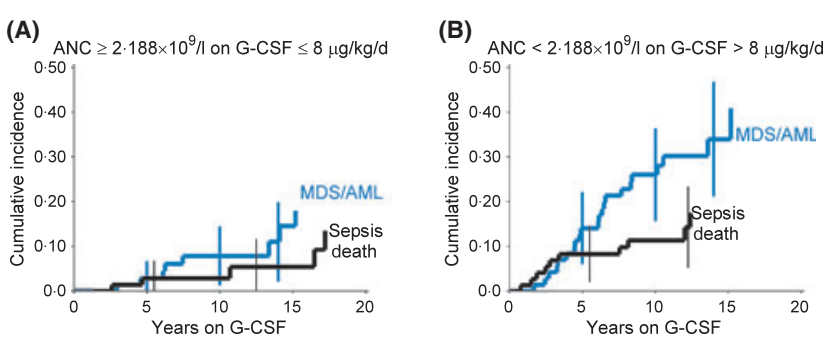

Fig 2. Cumulative incidence of MDS/AML and sepsis death in subgroups of SCN patients. All estimates are based on updated follow-up. Error bars show point-wise 95% confidence limits at selected years. (A) Cumulative incidence of MDS/AML (blue curve) and sepsis death (black curve) among patients who achieved an adequate mean absolute neutrophil count (ANC) by months 6–18 (≥2.188 cells × 10^9/l) at doses of G-CSF less than or equal to 8 μg/kg per d). (B) Corresponding cumulative incidence curves among patients who failed to achieve an adequate ANC despite higher doses of G-CSF.

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Authors contributions

PSR, CZ, KW, DCD, PN, and BPA designed the study; PSR analysed the data; PSR and CZ wrote the paper; AAB and CZ set the database; CZ, MAB, LAB, YD, SK, KW, and DCD were involved in patient care; all participated in writing the paper.

Disclosures

David C. Dale has research support from Amgen, and is a consultant and speaker for Amgen (Honorarium). Laurence A. Boxer owns Amgen stock.

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