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Case report

Lenalidomide monotherapy and in combination with cytarabine, daunorubicin and etoposide for high-risk myelodysplasia and acute myeloid leukaemia with chromosome 5 abnormalities

M. Dennis [a,*], D. Culligan [b], D. Karamitros [c], P. Vyas [c], P. Johnson [d], N.H. Russell [e], J. Cavenagh [f], A. Szubert [g], S. Hartley [g], J. Brown [g], D. Bowen [h]

[a] Christie Hospital, Manchester, United Kingdom
[b] Aberdeen Royal Infirmary, Aberdeen, United Kingdom
[c] John Radcliffe Hospital, Oxford, United Kingdom
[d] Western General Hospital, Edinburgh, United Kingdom
[e] Nottingham University Hospital, Nottingham, United Kingdom
[f] St. Bartholomew's Hospital, London, United Kingdom
[g] Clinical Trials Research Unit, University of Leeds, Leeds, United Kingdom
[h] St. James's Institute of Oncology, Leeds, United Kingdom

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ABSTRACT

Patients with high risk myelodysplasia (HR-MDS) and acute myeloid leukaemia (AML) with chromosomal changes involving deletion of the long arm of chromosome 5 (del5q), especially with complex karyotype, rarely have a durable response to combination chemotherapy. In the subgroup with monosomal karyotype there are no long term survivors (Fang et al., 2011) [1]. Recent experience indicates that the incidence of del5q in AML is ~20–30%, with only 20–25% of patients achieving complete remission (CR) (Farag et al., 2006) [2]. Additionally, therapy has significant toxicity, with induction death rates ~20% even in younger patients (Juliusson et al., 2009) [3]. This lack of efficacy provides the clinical rationale for combination/sequential therapy with Lenalidomide and combination chemotherapy. Dose dependent haematological toxicity is the major safety concern with such a combination protocol. Therefore we conducted a phase 2 study, AML Len5 (ISRCTN58492795), to assess safety, tolerability and efficacy of lenalidomide monotherapy, followed by lenalidomide with intensive chemotherapy in patients with primary/relapsed/refractory high risk MDS or AML with abnormalities of chromosome 5.

Patients with high risk myelodysplasia (HR-MDS) and acute myeloid leukaemia (AML) with chromosomal changes involving deletion of the long arm of chromosome 5 (del5q), especially with complex karyotype, rarely have a durable response to combination chemotherapy. In the subgroup with monosomal karyotype there are no long term survivors [1]. Recent experience indicates that the incidence of del5q in AML is ~20–30%, with only 20–25% of patients achieving complete remission (CR) [2]. Additionally, therapy has significant toxicity, with induction death rates ~20% even in younger patients [3]. Conversely, patients with low risk MDS and del5q can respond dramatically to lenalidomide at conventional doses [4,5]. Thus, studies have investigated lenalidomide therapy in AML/HR-MDS. A phase 2 study of lenalidomide in HR- MDS with the del5q abnormality (alone or with other cytogenetic abnormalities) indicated a 20% CR rate with lenalidomide 10 mg once a day, escalated to 15 mg in suboptimally responding patients. However, all responders had isolated del5q [6]. Subsequent studies have evaluated escalating doses up to 50 mg daily but response rates remained ~4% [7]. A phase 1 study in relapsed/refractory AML patients also indicated that lenalidomide can be tolerated up to 50 mg daily, but there were no CR's in the del5q population. Those that did respond had low presenting white cell counts suggesting limited efficacy as monotherapy in proliferative disease [8] Additionally, the Nordic group had similar findings when they assessed lenalidomide monotherapy up to 20 mg daily in a phase 2 study for MDS/AML patients with any form of chromosome 5 abnormality and noted no response in patients with TP53 mutation [9]. More recently a phase 1 study of sequential therapy with azacitidine and lenalidomide has identified an alternative approach capable of inducing haematological improvement and complete cytogenetic remissions, although has significant haematological toxicity [10].

This lack of efficacy provides the clinical rationale for combination/sequential therapy with Lenalidomide and combination chemotherapy. As already outlined dose dependent haematological

* Corresponding author. Tel.: +44 161 446 8420.
E-mail address: mike.dennis@christie.nhs.uk (M. Dennis).

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toxicity is the major safety concern with such a combination protocol. Therefore we conducted a phase 2 study, AML Len5 (ISRCTN58492795), to assess safety, tolerability and efficacy of lenalidomide monotherapy, followed by lenalidomide with intensive chemotherapy in patients with primary/relapsed/refractory high risk MDS or AML with abnormalities of chromosome 5.

Patients were considered eligible if they had a diagnosis of primary/relapsed/refractory AML (as defined by WHO 2008) or high risk MDS (defined as IPSS INT-2/High) with chromosome 5 cytogenetic abnormalities (including del5q) and were suitable for intensive chemotherapy. Cytogenetic analysis was undertaken at regional specialist cytogenetic laboratories using conventional chromosome G-banding on bone marrow cultures. Specific FISH analysis for del5 q was not undertaken.

The main exclusion criteria were prior use of lenalidomide or other investigational agents within the last 4 weeks. Composite primary endpoint was early death rate (defined as death within 30 days of starting combination therapy) and survival with platelet recovery ($>100\times10^9$/l) 42 days after the last dose of course one combination therapy. If treatment was found to be safe and acceptable, the CR rate (CR/CR with incomplete haematopoietic recovery) was assessed at day 21 post the last cycle of combination chemotherapy, and used to determine the sample size for the study. A four-stage phase II non randomised trial design (Sargent) was used to incorporate the possibility that the trial might be inconclusive based on the observed CR rate. Stopping rules were included at four time points; after 10, 19, 30 and all 39 patients had completed the first course of combination chemotherapy. For patients recruited with $\geq 5\%$ blasts, further stopping rules were specified as follows for lenalidomide monotherapy: more than 20% having a treatment-related death; more than 30% withdrawn due to delayed recovery of blood counts with hypoplastic bone marrow.

All patients were recruited and consented from 6 UK leukaemia centres. The treatment schedule was designed such that all patients would receive an initial cycle of lenalidomide monotherapy 10 mg daily on days 1–21 of a 28-day cycle. Remission status was then assessed from a day 28 bone marrow.

Responses were defined as; CR $<5\%$ blasts in the bone marrow and haematopoietic recovery. CR with incomplete haematopoietic recovery (CRi) fulfilling all criteria for CR except for haematopoietic recovery.

Partial Response (PR) $\geq 5\%$ blasts in the bone marrow but blasts having reduced by $\geq 50\%$ from baseline. No Response (NR) $<50\%$ blast reduction in the bone marrow from baseline.

Patients who had presented with HR-MDS ($<$ 5% blasts) and had no blast excess at day 28 and who also achieved haematopoietic recovery, received further 28 day cycles of lenalidomide monotherapy 10 mg daily on days 1–21. After receiving 3 cycles of lenalidomide monotherapy, patients in remission were considered for allogeneic stem cell transplant. If transplant were not an option then patients would continue with maintenance lenalidomide.

Patients who presented with HR-MDS or AML ($\geq 5\%$ blasts) who at day 28 had achieved a PR could receive a second cycle of lenalidomide monotherapy. If CR or no response at day 28, then patients progressed to combination chemotherapy with Lenalidomide administered at 10 mg once daily for 10 days concurrently

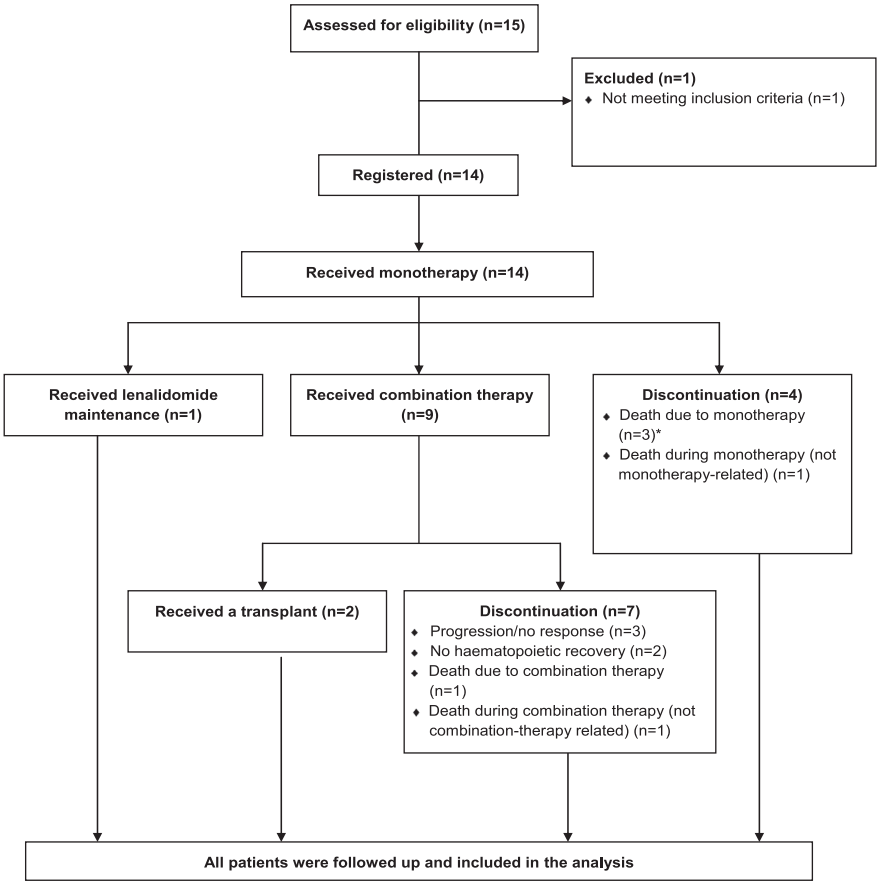

Fig. 1. *Includes one patient who after lenalidomide monotherapy only received a single dose of ADE but no lenalidomide as combination therapy as the patient was nil by mouth. As recommended by the DMEC, this patient was not considered as receiving combination therapy.