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Toxicity profile of the immunomodulatory thalidomide analogue, lenalidomide: Phase I clinical trial of three dosing schedules in patients with solid malignancies

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ABSTRACT

Thalidomide is an anti-angiogenic agent currently used to treat patients with malignant cachexia or multiple myeloma. Lenalidomide (CC-5013) is an immunomodulatory thalidomide analogue licensed in the United States of America (USA) for the treatment of a subtype of myelodysplastic syndrome. This two-centre, open-label phase I study evaluated dose-limiting toxicities in 55 patients with malignant solid tumours refractory to standard chemotherapies. Lenalidomide capsules were consumed once daily for 12 weeks according to one of the following three schedules: (I) 25 mg daily for the first 7 d, the daily dose increased by 25 mg each week up to a maximum daily dose of 150 mg; (II) 25 mg daily for 21 d followed by a 7-d rest period, the 4-week cycle repeated for 3 cycles; (III) 10 mg daily continuously. Twenty-six patients completed the study period. Two patients experienced a grade 3 hypersensitivity rash. Four patients in cohort I and 4 patients in cohort II suffered grade 3 or 4 neutropaenia. In 2 patients with predisposing medical factors, grade 3 cardiac dysrhythmia was recorded. Grade 1 neurotoxicity was detected in 6 patients. One complete and two partial radiological responses were measured by computed tomography scanning; 8 patients had stable disease after 12 weeks of treatment. Fifteen patients remained on treatment as named patients; 1 with metastatic melanoma remains in clinical remission 3.5 years from trial entry. This study indicates the tolerability and potential clinical efficacy of lenalidomide in patients with advanced solid tumours who have previously received multi-modality treatment. Depending on the extent of myelosuppressive pre-treatment, dose schedules (II) or (III) are advocated for large-scale trials of long-term administration.

1. Introduction

Lenalidomide is a thalidomide analogue currently in clinical development for the treatment of a variety of oncological and inflammatory diseases.[1] The parent compound, thalidomide, is used in the treatment of moderate to severe erythema nodosum leprosum (ENL) and less frequently in the treatment of a wide range of other clinical conditions refractory to standard

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therapies.[2,3] These conditions include rheumatoid arthritis,[4] the inflammatory and wasting effects of chronic tuberculosis,[5] Behcet's disease,[6] Crohn's disease,[7–9] aphthous ulcers,[10–12] cachexia associated with HIV infection[13,14] and AIDS-related Kaposi's sarcoma.[15] There is an increasing clinical evidence base for the use of thalidomide as a treatment for multiple myeloma.[16–21] The role of thalidomide at conventional doses in the treatment of solid malignancies is less clear, particularly in view of the somnolence, constipation, venous thromboembolism, peripheral neuropathy and fatigue associated with treatment.[22–28]

Thalidomide analogues currently in clinical development, a class of agents known as the immunomodulatory drugs (IMDs or IMiDs), co-stimulate T-cells[29,30] and demonstrate anti-angiogenic activity[31] in preclinical models. The ability to co-stimulate T-cells has been associated with an increased Th1-type cytokine response and may contribute to anti-tumour activity *in vivo*.[32] In support of this hypothesis, IMDs have been shown to augment anti-tumour responses in preclinical models *in vivo*, leading to sustained protection from malignant challenge[33] and in cells cultured *ex vivo* from patients with multiple myeloma.[34]

The IMD, lenalidomide (CC-5013 or IMiD3), has been administered to patients with multiple myeloma and myelodysplastic syndrome (MDS) in clinical trials.[1,35,36] The US Food and Drug Administration has approved lenalidomide for the treatment of subjects with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a 5q deletion cytogenetic abnormality with or without additional cytogenetic abnormalities. The recommended starting dose is 10 mg/d. Lenalidomide is currently the lead IMD for clinical trials in the treatment of haematological and solid malignancies. Phase I–II clinical data suggest that treatment is well tolerated by patients with multiple myeloma in 25 mg and 30 mg cyclic therapy regimens (i.e. treatment for 3 weeks in a 4-week cycle) and there are suggestions of clinical efficacy in treating this condition.[35] The most common serious adverse events were neutropaenia (grade 3 in 60%; grade 4 in 16%) requiring growth factor support and thrombocytopenia (grade 3 in 20%) at doses of 50 mg/d. The authors suggested that the maximum tolerated dose (MTD) in patients with multiple myeloma was 25 mg/d. Five phase III trials of lenalidomide treatment in combination with standard therapies are currently ongoing in patients with multiple myeloma.[1]

Since patients with solid malignancies such as renal cell carcinoma may be exposed to multiple regimes of combination chemotherapy, immunomodulatory treatments and radiotherapy, it cannot be assumed that they will develop the same degree of myelosuppression on lenalidomide treatment as patients with multiple myeloma. A phase I study of lenalidomide in 20 patients with solid malignancies (metastatic malignant melanoma, pancreatic adenocarcinoma, renal cell carcinoma, breast carcinoma, carcinoid and squamous cell lung carcinoma) has demonstrated the feasibility of accelerated dose titration over a 4-week period and has provided preliminary data on the tolerability of longer term administration in 4 patients.[37] Although 7 patients developed serious adverse events, the investigators did not associate them with treatment and the MTD was not defined.

Since the optimal dose schedule for longer term administration of lenalidomide in patients with advanced solid malignancies is currently not clear, we performed a multi-centre, open-label phase I study in 55 patients. This study had two aims: firstly to determine the MTD by dose escalation; and secondly to study the tolerability of two dosing regimes over a 12-week period.

2. Patients and methods

2.1. Patient selection

Patients were recruited at 2 oncology centres in the United Kingdom (UK) (St George's Hospital, London, and the University Hospitals of Leicester) according to the following eligibility criteria: histological or cytological evidence of solid malignancy that had not responded to standard therapy; measurable disease by radiological criteria; clinical or radiological evidence of disease progression in the 3 months prior to trial entry; life expectancy over 2 months; adequate baseline organ function; minimum body weight of 50 kg. Previous treatment with chemotherapy or radiotherapy was permitted, with the exception of radiotherapy to the brain. Patients were excluded if they offered a history of hypersensitivity to thalidomide or similar drugs, if they had evidence of another active malignancy or if they had received anti-cancer therapy or experimental treatment within the previous 30 d. Women were excluded from the study if pregnant, lactating or not using adequate contraception. The study protocol was approved by the local research ethics committee. The trial was conducted according to current international good clinical practice guidelines and in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients prior to participation in the study.

2.2. Treatment and assessment

Lenalidomide (see Fig. 1) was supplied in 5 mg and 50 mg hard gelatin capsules by Celgene Corporation (Warren, NJ, United States of America (USA)). The prescribed dose of lenalidomide was taken as a single dose each morning. Patients were instructed not to consume any food for 2 h before and 2 h after each daily dose. The capsules were swallowed with tap water.

Three dose regimes were adopted, as shown in Fig. 2. The intra-patient dose escalation for cohort I was based on contemporary oncology trial design;[37,38] the principal aim of this design was rapid assessment of potential dose-limiting toxicity (DLT) and defining the MTD. Following completion of serial recruitment of patients to cohort I, randomised recruitment to cohorts II and III was concurrent. The aim of the trial design adopted in the latter two cohorts was to assess

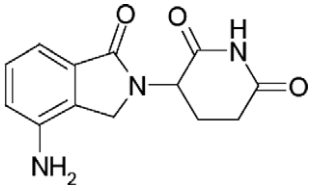

Fig. 1 – Chemical structure of lenalidomide.

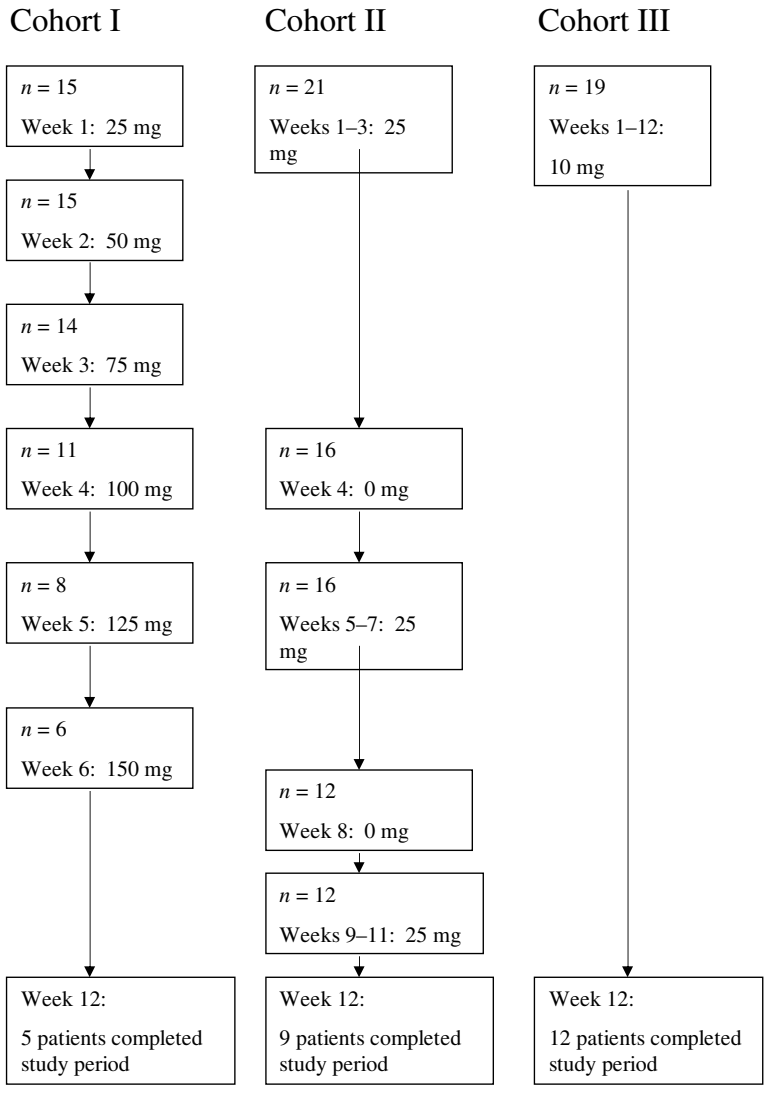

Fig. 2 – Flow chart of dose regimes for cohorts I, II and III and numbers of patients entering each dose level. Numbers (*n*) refer to total number of patients commencing each dose level at the time-points shown. Patients were recruited concurrently to cohorts II and III by randomisation. Dose shown in each box refers to daily dose of lenalidomide consumed by each patient at that dose level. For dose modifications during treatment, see main text.

the tolerability of a dose schedule that could be administered up to or beyond 12 weeks. The selected dose regimes were based on results from cohort I, clinical data from healthy volunteers and phase I clinical trial data from patients with solid malignancies.[37]

Before initiation of therapy, patients were subject to complete medical history, physical examination (including detailed neurological examination) and baseline tests. Once administration of the study drug started, patients were reviewed at weekly intervals. Assessment of toxicity in clinical evaluation and laboratory tests was scored by the National Cancer Institute (NCI)-Common Toxicity Criteria (http://ctep.info.nih.gov/reporting/ctc.html). At the discretion of the investigator, patients in cohort I demonstrating toxicity were permitted to have their daily dose reduced by 25–50 mg daily. In cohorts II and III, neither dose adjustments nor delays were permitted during the first 4 weeks of treatment; dose reduction was permitted after 4 weeks of treatment if the patient experienced grade 3 toxicity. In all three cohorts, if a patient suffered DLT definitely associated with the trial drug, treatment was stopped. DLT was defined as grade 3–4 non-haematological toxicity or grade 4 haematological toxicity. The MTD was defined as the dose level below the dose at which DLT was recorded in a third or more of the patients treated at that dose level. Serious adverse events (SAEs) were defined as in-patient admissions, life-threatening events or important medical events that may, in the judgement of the investigator, result in death or life-threatening situation. In the opinion of the investigator, if clinical benefit and an acceptable safety review were demonstrated at the end of the 12-week study period, the individual was offered the opportunity to continue treatment as a 'named patient' up to a total of 54 weeks at the initial dose or at the daily dose they were consuming at the end of the 12-week study period.

On account of reports from other trials of potential effects on electrocardiogram (ECG) parameters of heart rhythm

(Investigator's Brochure 2004, Celgene Corporation), the QTc interval was measured in all patients before treatment and every other week or twice weekly during treatment. QTc measurement was performed by ECG computer readout; when this facility was not available, it was calculated manually from ECG tracings. In adult males, a borderline QTc time was defined as a value between 431 and 450 ms; values greater than 450 ms were defined as prolonged. In adult females, borderline values were defined as 451–470 ms; prolonged was defined as greater than 470 ms.

Evaluation of tumour response compared with baseline was performed following 12 weeks of treatment by computed tomography (CT) scanning and measurement of lesions using Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[39] 'Named patients' who remained on treatment beyond 12 weeks had repeat imaging performed at the discretion of the investigator.

2.3. *Statistical analysis*

Data compilation and quality assurance review were performed by Harrison Clinical Research (Ely, UK). Data from all patients who received one or more doses of drug were included in the analyses. Simple descriptive statistics were used to analyse the data and no distinctions were made between different analysis populations.

3. Results

3.1. *Patient characteristics*

In cohort I, 15 patients received the study medication. Malignant diagnoses are listed in Table 1. Thirteen patients had stage IV cancer at screening and 2 patients had stage III cancer. Four subjects were female and 11 subjects were males. The patients' ages ranged from 31 to 74 years (mean 54 years).

Twenty-one patients were included in cohort II and 19 patients in cohort III. The distribution of genders in both cohorts was approximately even (21 males, 19 females). Malignant diagnoses are shown in Table 1 and anticancer treatments received by the patients prior to trial entry are shown in Table 2. In cohort II, all patients had stage IV cancer. In cohort III, 12 patients had stage IV cancer at screening, 5 patients had stage III cancer and 2 patients had inoperable stage II disease. Mean ages (and ranges in parentheses) for cohorts II and III were 53 (21–77) and 56 (17–74) years, respectively.

Table 1 – Malignant diagnoses of patients recruited: number of patients in each cohort

Cohort	I	II	III
	(*n* = 15)	(*n* = 21)	(*n* = 19)
Malignant melanoma	7	9	7
Renal cell carcinoma	4	3	4
Pancreatic carcinoma	0	1	1
Other carcinoma	3	6	5
Mesothelioma	1	1	2
Sarcoma	0	1	0

Table 2 – Previous treatment received by patients recruited

Cohort	I	II	III
	(*n* = 15)	(*n* = 21)	(*n* = 19)
Adjuvant chemotherapy	2	6	2
First-line palliative chemotherapy	6	11	7
Second-line palliative chemotherapy	3	4	3
Third-line palliative chemotherapy	3	0	1
Radiotherapy	6	13	4
Systemic immunotherapy	7	10	5
Thalidomide therapy	5	2	0
Other drug therapy (including experimental)	2	5	7

Numbers represent the number of patients in each cohort who had received a form of the treatment described. Chemotherapy refers to cytotoxic agents.

3.2. *Doses administered*

In cohort I, 6 patients completed the full weekly dose escalation of lenalidomide from 25 mg daily to 150 mg daily (see Fig. 2), 1 of whom did not complete the 12-week study period. In 4 patients, the daily dose was reduced by 25–50 mg daily due to reduced white blood cell counts; four patients had a dose reduction due to other adverse events (AEs) (see below). In 2 patients, the dose was reduced by the investigator secondary to provisional safety information made available from ongoing trials of lenalidomide treatment for multiple myeloma. In the opinion of the investigator, at the end of the 12-week study period, 2 patients were benefiting clinically from lenalidomide treatment and were permitted to continue treatment on a named patient basis. The mean treatment duration for patients in cohort I was 6.8 weeks.

Twenty-one patients were treated in cohort II and 19 patients in cohort III (for doses administered, see Fig. 2). The mean treatment duration for patients in cohort II was 7.7 weeks and for cohort III it was 9 weeks. At the end of the study period, 6 patients from cohort II and 7 patients from cohort III continued treatment at the same dose as named patients.

3.3. *Toxicity in cohort I*

In cohort I, 173 AEs were recorded in 15 patients from the screening visit until the end of the study period, of which 28 occurred prior to administration of the study medication. The incidence of AEs per patient shown in Table 3 is lower than the corresponding figures for the subsequent 2 cohorts since only 5 out of 15 patients completed the 12-week study period. With regard to the relationship of events to the study medication, events were classified as probable (20 AEs), possible (66 AEs), remote (65 AEs) and unclear (21 AEs). For 50% of the AEs, the intensity was classified as mild, 44% were moderate and 6% were severe. The highest rate of AEs was found in the 125 mg/d dose group (20%). The system organ classes for all dose levels were: general disorders (15% of

Table 3 – Overview of adverse events

Cohort	I	II	III
Patients treated	15	21	19
Number of adverse events	173	151	103
Adverse events per patient[a]	2.1	7.2	5.4
Serious adverse events	15	12	10
NCI Grade 1/2 events	139	129	89
NCI Grade 3/4 events	19	15	13

NCI, National Cancer Institute.
a For discussion of the values in this row, see Results section of main text.

AEs); respiratory, thoracic and mediastinal disorders (15% of AEs); nervous system disorders (13% of AEs); gastrointestinal disorders (12% of AEs). Lethargy was commonly recorded in the first 5 weeks of treatment.

At screening visit for cohort I, 1 patient had previously undiagnosed ECG abnormalities (left ventricular hypertrophy and sinus bradycardia) and 2 had borderline QTc intervals (for definitions, see Methods section above). During treatment in cohort I, the mean QTc interval increased from 421 ms to 440 ms at the end of the study period. An increase in QTc interval to borderline or abnormal levels after 4 weeks of treatment was recorded in 2 patients: in 1 patient, the drug was discontinued due to progressive malignant disease; in the other patient, the trial drug was continued for the rest of the study period without adverse effect, and subsequent normalisation of the QTc interval was recorded. One patient with a normal ECG and QTc interval at screening was noted to be in atrial fibrillation during hospital admission for neutropaenia requiring medical therapy. Prior to trial entry, this patient had a past medical history of transient ischaemic attacks requiring lifelong treatment with warfarin. At the time of the event, serum biochemistry values were normal; thyroid function tests were not recorded. Relationship with study drug was classified as 'possible'. Stopping the trial drug for 7 d did not affect this condition; the trial drug was continued without adverse effect and serial ECGs thereafter demonstrated sinus rhythm. No change in this patient's QTc interval was recorded. With regard to neurotoxicity, grade 1 impairment of pinprick or light touch sensation was recorded in 4 patients in cohort I during treatment compared with pretreatment examination. In 1 patient, a grade 1 skin rash had the appearance of radiation recall erythema 6 weeks after previous radiotherapy.

Serious adverse events (SAEs) occurred in the 25, 75, 100 and 125 mg/d dose groups, with no obvious dose dependency. The causal relationship of one SAE to the test medication was definite: 1 patient at the first dose level (25 mg/d) developed a grade 3 hypersensitivity rash and was therefore withdrawn from the study. Neutropaenia was the most frequent SAE. It was recorded in 4 patients: in 2 patients during administration of 25 mg/d (grades 2 and 4) and in 2 patients during administration of 75 and 100 mg/d (both grade 4). Symptomatic grade 2 anaemia requiring blood transfusion was recorded in 2 patients. Dyspnoea occurred twice in 2 patients during administration of lenalidomide; the causal relationship with the trial drug was classified as 'possible' in both cases, since both patients had disease-related pleural effusions and 1 patient had signs of a chest infection in the absence of neutropaenia. One patient required hospital admission for the treatment of grade 3 dehydration; the relationship with the trial drug was classified as 'remote'.

At the end of the 12-week study period, 1 patient continued treatment as a named patient. After 1 month of treatment, this patient developed progressive malignant disease, complicated by a deep venous thrombosis, and was withdrawn from the named patient programme.

In summary, the principal toxicity of lenalidomide treatment in cohort I was observed in haematological laboratory values. Although erythrocyte, haemoglobin and haematocrit values were below the normal range for the majority of measurements before and during the study period, no effect of treatment was observed on these values and the levels were therefore thought to reflect underlying disease rather than drug toxicity. Contrastingly, leukocyte and neutrophil levels began to fall from week 3 of treatment and demonstrated a progressive decline with treatment time. Treatment effects were not observed on lymphocytes, monocytes or basophils. Platelet counts were diminished (grade 2 toxicity) in 4 patients between weeks 3 and 9 of treatment. No significant toxic effects were observed in serial serum biochemistry measurements.

3.4. *Toxicity in cohorts II and III*

Based on the data from cohort I, it was decided to study two dosing regimes in more detail over a 12-week period with a view to assessing the feasibility of longer term administration. Patients in cohort II received 25 mg daily in a cyclic regimen (see Fig. 2) and the patients in cohort III received 10 mg daily continuously. Out of a total of 40 patients recruited, 21 patients completed the 12-week treatment period per protocol as shown in Fig. 2. Three patients were withdrawn from the treatment protocol due to SAEs (see below) and 7 patients for other AEs. Six patients developed disease progression during the study period. Two patients died during the study period: 1 patient (cohort II) had progressive malignant disease and 1 patient (cohort II) developed fatal pneumonia in the absence of neutropaenia. One patient (with a single kidney) was withdrawn from the study by the investigator on account of a grade 1 rise in the serum creatinine level.

In cohorts II and III, a total of 254 adverse events were recorded (see Table 3). The mean incidence of AEs per patient was 7.2 AEs in cohort II and 5.4 AEs per patient in cohort III. The causal relationship of two adverse events to the test medication was definite in 2 patients in cohort II: 1 patient developed a grade 3 allergic rash and 1 patient developed grade 3 neutropaenia. In total, 43% (65 events) of the AEs in cohort II and 27% (28 events) in cohort III were classified as probably or possibly drug related. The system organ classes with the highest incidence of AEs were gastrointestinal disorders (19% of AEs), general disorders (13%), nervous system disorders (11%), skin and subcutaneous tissue disorders (11%), investigations (10%), respiratory, thoracic and mediastinal disorders (9%) and musculoskeletal and connective tissue disorders (7%). Decreased haemoglobin levels were observed in 2 patients (cohort II), although no thrombocytopenia was

recorded. With regard to the severity of AEs, similar proportions were recorded in both cohorts: In cohort II, 52% of the AEs were classified as mild, 39% as moderate and 9% as severe; in cohort III, 46% were mild, 45% moderate and 10% severe.

One patient had a prolonged QTc interval at screening, which was not deemed clinically significant and did not alter significantly during treatment. Excluding this patient from the analysis, the mean QTc time increased from baseline until the final examination in both cohorts. In cohort II, the mean QTc time increased from 374 ms at baseline to 430 ms at the final examination. In cohort III, the mean QTc time increased from 383 ms at baseline to 433 ms at the final examination. One patient in cohort III, with no past medical history of cardiac disease, developed a grade 3 dysrhythmia (supraventricular tachycardia) on the third day of an in-patient admission for nausea and vomiting requiring medical intervention. Blood tests preceding the onset of the event demonstrated uraemia and hypernatraemia. Thyroid function tests were not recorded. Following intravenous rehydration, no further episodes of dysrhythmia occurred. Trial therapy was terminated during this hospital admission. With regard to neurotoxicity, grade 1 impairment of pinprick or light touch sensation was recorded in 2 patients and grade 1 impairment of muscle strength, tone or reflexes was noted in 9 patients during treatment compared with pre-treatment examination.

Twenty-two adverse events were classified as serious. Twelve SAEs occurred in cohort II and 10 in cohort III. Although the rate of Grade 3 or 4 events was similar for both cohorts (see Table 3), the most frequent grade 3/4 event was neutropaenia (4 events), all of which occurred in cohort II. None of these episodes were associated with sepsis. The development of a grade 3 allergic skin rash in 1 patient in cohort II was classified as definitely related to the study medication. One patient in cohort II was admitted with grade 2 dehydration and constipation, which was possibly treatment related. The relationship of a cerebral haemorrhage in 1 patient in cohort II and a grand mal seizure in 1 patient in cohort III to the study medication were classified as 'remote' by the investigators. Similarly, the development of a tension pneumothorax in 1 patient in cohort III was not thought to be treatment related.

At the end of the 12-week study period, 6 patients in cohort II continued treatment as named patients for 3–10 months. Two SAEs were recorded: 1 patient was admitted to hospital due to abdominal pain 10 months into the long-term safety study and was found to have progressive intra-abdominal malignant disease; another patient developed grade 3 neutropaenia 5 months into treatment in the long-term safety study, requiring a dose reduction. In cohort III, 7 patients remained on 10 mg of lenalidomide daily as named patients for 2 months to 3+ years. Three SAEs have been recorded in 3 out of 7 patients: grade 3 autoimmune hypothyroidism; grade 3 neutropaenia (without sepsis); sepsis resulting in death (in the absence of neutropaenia).

In summary, as in cohort I, the principal toxicity of treatment in cohorts II and III was observed in haematological laboratory values. Although haemoglobin and haematocrit values were below the normal range for the majority of measurements before and during the study period, no effect of treatment was observed on these values and the levels were therefore thought to reflect underlying disease rather than drug toxicity. Contrastingly, leukocyte and neutrophil levels demonstrated a slight decline with treatment time, with greater severity in cohort II than cohort III. Treatment effects were not observed on lymphocyte, monocyte, basophil or platelet counts. No significant toxic effects were observed in serum biochemistry measurements: grade 1 toxicity was observed in 3 patients, all values thought to be disease related.

3.5. *Clinical efficacy*

CT scans of marker malignant lesions were measured after 12 weeks of treatment and compared with baseline imaging using RECIST criteria. Of 3 patients who had imaging performed as per protocol in cohort I, 1 patient had stable disease recorded after 12 weeks of treatment. In cohort II, 2 patients were found to have partial responses and 3 patients had stable disease. In cohort III, 1 patient with metastatic malignant melanoma was found to have a complete response and 5 patients had stable disease. In the long-term safety study extension, 1 patient in cohort II and 1 patient in cohort III remained clinically and radiologically stable for 10 months. At the time of reporting, 1 patient in cohort III remained on lenalidomide treatment in complete clinical response 3.5 years from commencing the long-term safety study.

4. Discussion

This large phase I study employing three different dose schedules provides toxicity data on a drug which is currently in large-scale clinical trials and is approved in the USA for the treatment of chronic anaemia in a subpopulation of patients with MDS. In addition to its potential role in the treatment of multiple myeloma and MDS, it is conceivable that lenalidomide may be a useful treatment for solid malignancies such as malignant melanoma, prostate adenocarcinoma or renal cell carcinoma. In this regard, detailed toxicity data in relevant patient groups is crucial to its clinical advancement.

The results from cohort I of this trial demonstrated that daily doses of lenalidomide equal to or greater than 75 mg can result in significant myelosuppression. Although thrombocytopenia was also observed, it was the severity of neutropaenia induced by the treatment that proved dose limiting. A parallel can be drawn between this finding and the phase I trial results in patients with multiple myeloma, in whom neutropaenia and thrombocytopenia were observed at daily doses equal to or greater than 50 mg, leading the investigators to suggest that that the MTD in that patient group was 25 mg/d.[35] In general, the degree of myelosuppression observed in this trial of patients previously treated with a wide range of modalities for solid malignancies (as shown in Table 2) was less than that observed in patients with refractory multiple myeloma.[35] In the study presented here, the MTD was not established in the dose-escalation design of cohort I since a sufficiently high incidence of neutropaenia was not observed at any dose level.

Based on the data from cohort I, recruitment to cohorts II and III was performed concurrently to compare the clinical feasibility of two dosing schedules that could be adopted in

large-scale trials of longer term treatment with lenalidomide. The dose regime adopted in cohort II over a 12-week period resulted in four episodes of grade 3 or 4 neutropaenia. Neutropaenic sepsis was not observed. Although the dose schedule adopted for cohort III did not result in any significant neutropaenia, it should be noted that the patients in cohort II were more heavily pre-treated with chemotherapy, immunotherapy and radiotherapy than the subjects in cohort III (see Table 2). SAEs other than neutropaenia were recorded at similar frequencies in cohorts II and III. The incidence rate of neutropaenia in cohort II was not dose limiting. Overall, the results suggest that the dose regimes adopted for cohorts II and III are well-tolerated by patients with solid malignancies who have previously received multiple standard therapies, although the schedule used in cohort II is more likely to require dose modification during longer term administration to heavily pre-treated patients.

The increase in mean QTc interval measured on serial ECG tracings over the 12-week treatment period was not associated with the recording of adverse cardiac events. The methods used in this trial to calculate the QTc interval have been superseded by 'real time' QTc monitoring, which has been employed in larger scale trials of lenalidomide (Investigator's Brochure 2006, Celgene Corporation). As suggested by the results presented above, systematic testing of the measurement of the QTc interval has confirmed its lack of value in predicting cardiotoxicity associated with symptoms (i.e. grade 2 toxicity) or symptoms requiring intervention (i.e. grade 3 toxicity): its measurement in future trials is not recommended. In the trial presented here, 1 patient with a history of cardiovascular disease being treated at the lowest dose level (25 mg/d) of cohort I experienced palpitations in the first week of treatment and was found to have atrial fibrillation during hospital admission. The trial drug was continued without adverse effect. One patient in cohort III receiving 10 mg of lenalidomide daily developed supraventricular tachycardia during in-patient admission for nausea and vomiting. Although this patient had no cardiac history of note, predisposing serum electrolyte abnormalities were noted during the in-patient admission prior to the cardiac event. Trial therapy was terminated during the hospital admission. Since both patients had predisposing factors for cardiac dysrhythmia, a definite association with the trial drug cannot be established. Large scale, randomised studies would be necessary to assess whether dysrhythmia is more common in individuals on lenalidomide treatment who have predisposing factors for cardiac disease.

Although clinical efficacy end-points were not primary objectives of this study, all patients in cohorts II and III had CT scanning performed to look for preliminary evidence of the potential utility of lenalidomide treatment in patients with a variety of advanced solid malignancies. The results provide some scope for early optimism, particularly the complete radiological response observed in 1 patient with metastatic malignant melanoma who has now been in complete clinical response for over 3 years and remains on the trial medication.

In summary, the data presented in the study described here clearly demonstrate that lenalidomide possesses a different toxicity profile from the parent compound, thalidomide, with significantly less somnolence, constipation and neurotoxicity.[21,28] In patients with solid malignancies refractory to standard therapies, dose escalation of lenalidomide has demonstrated that grade 3–4 neutropaenia occurs at daily doses of 75 mg or above. The sporadic and unpredictable occurrence of rash is dose limiting in a small number of patients. The suggestions of clinical activity and the tolerability profile demonstrated for both 10 mg/d and 25 mg/d continuous dosing advocate the advancement of lenalidomide to large-scale clinical trials in patients with solid malignancies.

Conflict of interest statement

AGD holds a research grant from, acts as a consultant for, and owns shares in Celgene. RAS, WPS, CAD and KOB have no financial or personal relationships which would act as conflicts of interest for publication of this study. RDK is employed by Celgene Corporation.

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