Amyloidosis and POMALIDOMIDE

<Pomalidomide_D>

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1. EXECUTIVE SUMMARY

- The use of Pomalyst (pomalidomide) for the treatment of amyloidosis is not an approved indication according to the Prescribing Information
- A prospective Phase II study investigated the use of pomalidomide and dexamethasone in 33 patients with previously treated light-chain amyloidosis (AL) (Dispenzieri et al. 2012)
    - Patients were administered pomalidomide 2 mg daily in 28-day treatment cycles along with dexamethasone 40 mg/wk orally. Non-responders were allowed to dose escalate to pomalidomide 4 mg/day. Thromboprophylaxis included aspirin (325 mg/day)
    - Hematologic responses to pomalidomide were reported in 47% of patients who had received prior treatment with lenalidomide and 43% of patients who had received prior treatment with bortezomib. A total of 5 patients had organ improvement (4 of 27 patients with cardiac involvement and 2 of 12 patients with renal involvement)
    - Among the 33 patients, 16 confirmed responders were reported with a median time to hematologic response and median duration of response (DOR) of 1.9 months (range, 0.9-11.3 months) and 19 months (95% CI: 8.3-NA), respectively
    - The most common Grade ≥3 adverse events at least possibly attributed to the pomalidomide/dexamethasone therapy were neutropenia (n=9) and fatigue (n=5)

2. BACKGROUND

AL is defined by a clonal population of bone marrow plasma cells that produce a monoclonal light chain of κ or λ type as either intact molecules or fragments (Gertz 2012). The misfolding of the light chain protein to form β-pleated sheets results in insoluble protein deposits in various tissues and interferes with organ function. One epidemiologic study estimated an incidence of 4.5 per 100,000. The inherited amyloidoses are rare, with an estimated incidence of less than 1 per 100,000 (Seldin et al. 2008).

3. SUMMARY OF CLINICAL EXPERIENCE

3a. Phase II Study: Pomalidomide/Dexamethasone

In a prospective Phase II study, **Dispenzieri et al.** investigated the use of pomalidomide and dexamethasone in patients with previously treated AL (Dispenzieri et al. 2012). Eligibility criteria included symptomatic relapsed or refractory amyloidosis with measurable disease as defined by any of the following: serum M-protein ≥ 1 g/dL, urine M-protein ≥ 200 mg/24 hours or serum Ig-free light chain ≥ 10 mg/dL along with an abnormal free light chain ratio. Patients were required to have an ANC ≥ 1000/ul, platelet count ≥75000/uL, a Cr ≤2.5 mg/dL and to have discontinued all chemotherapy regimens including investigational therapy for at least 2 weeks prior to registration. Patients were administered pomalidomide 2 mg/day for 28 days (1 cycle) along with dexamethasone 40 mg/wk orally. Thromboprophylaxis included aspirin (325 mg/day). Non-responders were allowed to dose escalate to pomalidomide 4 mg/day. Hematologic assessment and the toxicity profile were monitored monthly and echocardiography was performed every 3 months for patients with baseline cardiac involvement. Dose reductions were made according to the type of adverse event and attribution. Data analyses were based on an intent-to-treat method. The primary endpoint was confirmed hematologic response and secondary endpoints included OS, PFS, DOR and AE profile. A total of 33 patients were enrolled. Baseline characteristics are shown in Table 1.

Table 1. Baseline Characteristics (N=33)

Characteristic	Value‡
Age, Median (range)	66 (52-82)
Male, n (%)	19 (58)
Diagnosis to on-study, median (range) months	37 (0.9-104)
Prior regimens, median (range)	2 (1-8)
Alkylators, n (%)	30 (91)
Corticosteroids, n (%)	26 (79)
IMiD, n (%)	7 (21)
Proteasome inhibitors, n (%)	14 (42)
Prior ASCT,%	16 (48)
ECOG Performance Status (>1), n (%)	10 (30)
NY Heart Class (1/2), n (%)	18 (64)/10 (36)
Organs involved	
Heart,(%)	27 (82)
Kidney, n (%)	12 (36)
Liver, n (%)	1 (3)
Autonomic/peripheral Nerve, n (%)	2 (6)/6 (18)
Clonality (λ/κ), n (%)	21 (66)/11(34)
Creatinine, mg/dL (range)	1.0 (0.7-2.4)
Alkaline phosphatase, IU/L (range)	100 (54-367)
Serun Troponin, mcg/L (range)	.01 (0.01-0.12)
NT-proBNP,ng/L (range)	1639 (88-36498)
TroponinT/NT-proBNP Stage (I/II/III)†, (%)	3 (9)/21 (66)/8 (25)
Serum M-protein, g/dL	0 (0-2.0)
Urine M-protein, mg/24 hours (range)	0 (0-1278)
Involved Immunoglobulin free light chain, mg/dL (range)	17.6 (4.98-706)
FISH abnormal [a], n (%)	20 (61)
t (11;14), n (%)	12 (63)
Deletion 13q, n (%)	10 (30)
Deletion 17p, n (%)	2 (11)
Other, n (%)	2 (6)

Adapted from Dispenzieri et al. 2012

Key: ECOG=Eastern Cooperative Oncology Group; **FISH**=fluorescent in situ hybridization; **IMiD**=immunomodulatory drugs; **NT-proBNP**=N-terminal pro-brain natriuretic peptide

‡ Values given are median with range or number of patients with percent

†TroponinT/NT-proBNP Staging: using the cutoffs of troponin t of <0.035 ng/L and NT-proBNP<332 pg/L, Stage I is below threshold; Stage II one above the threshold and Stage III both above the threshold

[a] Fish not done in 10 patients

The median patient age was 66 years (range, 52-82 years) and 58% patients were males. The median number of organs involved was 1 (range, 0-3). Mayo Stage III disease (defined as having both troponin T≥ 0.035 mcg/L and an NT-proBNP ≥332 ng/L) was reported in 25% of patients.

Of the 33 patients, 16 were confirmed responders with a median time to hematologic response of 1.9 months (range, 0.9-11.3 months) and a median DOR of 19 months (95% CI: 8.3-NA). A summary of response rates is shown in Table 2.

Table 2. Response Rates in AL patients receiving Pomalidomide and Dexamethasone (N=33)

Confirmed Response Rates	48% (95% CI: 30-66)
CR, n (%)	1 (3)
VGPR, n (%)	5 (15)
PR, n (%)	10 (30)
SD, n (%)	11 (33)
N/A†, n (%)	2 (6)
Organ Response, n (%)	5 (15)
Heart Involvement (n=27), Response (%)	4 (15)
Kidney Involvement (n=12), Response (%)	2 (17)
Liver Involvement (n=1), Response (%)	0

Adapted from Dispenzieri et al. 2012

Key: CI=Confidence interval; **CR**=complete response; **N/A**=not available; **PR**=partial response; **SD**=stable disease; **VGPR**=very good partial response

† Patients discontinued treatment before first evaluation (n=1 each, death and refusal)

Hematologic responses to pomalidomide/dexamethasone were reported in 47% of patients who received prior lenalidomide and 43% of patients who received prior bortezomib. A total of 5 patients had organ improvement (4 of 27 patients with cardiac involvement; and 2 of 12 patients with renal involvement). No organ response was seen in the patient with liver involvement. All 5 patients with organ improvement also had hematologic response with 1 VGPR and 4 PR.

At a median follow up of 28.1 months (range, 14.1-37.8 months), 17 patients died, 6 of whom were on study. Among these 6 patients, 4 died from progressive AL, 1 patient from H1N1 infection and 1 from sudden death. The median OS was 27.9 months (95% CI: 14.6-NA) with a 12 month survival of 76% (95% CI: 62-92). Median PFS was 14.1 months (95% CI: 9.7-21.1) with a 12 month PFS of 59% (95% CI: 44-79). To evaluate the differences in OS between responders and non-responders a landmark analysis was performed at 3 months post study entry. Of the 32 patients alive at 3 months, 13 had a confirmed hematologic response and 19 did not achieve a confirmed response. The median OS values for non-responders and responders were 21 months and not attained, respectively. A second landmark analysis was performed with patients assessable by FLC (difference between Kappa and lambda >5 mg/dL) analysis. Of the 27 patients analyzed, 13 had a 50% decrease in FLC within the first 3 months of treatment. Patients with or without a 50% decrease had median OS of not attained and 27.9 months (95% CI: 9.8-NA), respectively (log rank *P*-value 0.64).

The most commonly reported Grade ≥3 AEs at least possibly attributed to the pomalidomide/dexamethasone therapy were neutropenia (n=9) and fatigue (n=5). The most commonly reported Grade ≥3 AEs regardless of attribution were hematologic (n=15), cardiovascular (n=10), infectious (n=9), metabolic/laboratory (n=7), and constitutional (n=6). Specifically, the most common Grade ≥3 adverse events were neutropenia (n=10), pneumonia/bronchitis (n=7), and fatigue (n=6). Thrombosis was reported in 2 patients.

Protocol directed increase in the pomalidomide dose was reported in 9 patients, including 8 increased to 4 mg due to lack of response. A total of 16 patients had pomalidomide dose reductions, most commonly

due to neutropenia (n=8). Dexamethasone was dose reduced in 27 patients with confusion/mood alteration (n=12) cited as the most common reason for reduction.

Additional details regarding AEs can be found in Table 3 below.

Table 3. Adverse Events Regardless of Attribution

Adverse Event†	Grade 3	Grade 4	Grade 5
Hematologic			
Neutropenia	6	4	0
Thrombocytopenia	2	0	0
Anemia	0	1	0
Constitutional			
Fatigue	5	1	0
Neurology			
Peripheral Sensory	1	1	0
Gastrointestinal			
Diarrhea	2	0	0
Dyspepsia/Dysphagia	1	0	0
Ascites	1	0	0
Perforation	1	0	0
Infection/Febrile Neutropenia			
Pneumonia/Bronchitis	5	1	1
Febrile Neutropenia	1	0	0
Sinus Infection	1	0	0
Cardiovascular			
Atrial Fibrillation/Tachycardia	4	0	0
QTC Internal Prolongation	1	1	0
Sinus Bradycardia	0	1	0
L Ventricular Failure	1	0	0
Congestive Heart Failure	1	0	0
Syncope Vasovagal	3	0	0
Thrombosis	1	1	0
Pulmonary			
Dyspnea	4	0	0
Pleural Effusion	1	0	0
Metabolic/Laboratory			
Hyponatremia	3	0	0
Hyperkalemia	1	1	0
Hyperuricemia	0	1	0
Hypokalemia	0	1	0
Lymphatics			
Edema Limbs	3	0	0
Musculoskeletal			
Fracture	1	0	0
Muscle Weakness	2	0	0
Hepatic			
Aminotransferase Increased	0	1	0
Pain			
Pain in chest	1	0	0
Pain	2	0	0
Renal/Genitourinary			
Creatinine Increased	1	0	0
Urinary Frequency	1	0	0
Dermatology/Skin			
Decubitus Ulcer	1	0	0
Coagulation			
INR Increased	2	0	0

Adapted from Dispenzieri et al 2012

†Common Terminology Criteria for Adverse Events version 3.0

4. LIST OF ABBREVIATIONS

AE(s)	adverse events
AL	immunoglobolin light chain amyloidosis
ANC	absolute neutrophil count
ASCT	autologous stem cell transplantation
CI	confidence interval
CR	complete response
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
FDA	U. S. Food and Drug Administration
FISH	fluorescent in situ hybridization
FLC	serum Ig free light chain
IMiD	immumomodulatory drugs
N/A	not available
NT-proBN	PN-terminal pro-brain natriuretic peptide
OR	overall response
OS	overall survival
PFS	progression free survival
PR	partial response
SD	stable disease
VGPR	very good partial response

5. REFERENCES

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