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REVIEW ARTICLE

Lenalidomide in solid tumors

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Abstract
Background Lenalidomide is a thalidomide analogue with immunomodulatory and anti-angiogenic properties that include altering cytokine production, activating T cells, and augmenting natural killer cell function. Lenalidomide is approved by the U.S. Food and Drug Administration (FDA) for single-agent treatment of myelodysplastic syndromes associated with a 5q deletion and as a combination therapy with dexamethasone for the treatment of multiple myeloma.
Methods All prospective phase I–III clinical trials and preclinical data published until October 2011 and relevant literature were reviewed.
Results In phase I and/or II studies of single-agent lenalidomide in patients with advanced cancer, responses were reported in patients with prostate, thyroid, hepatocellular, pancreatic, and renal cancer and melanoma. The most common toxicities were hematologic, and in the first clinical trials, thrombotic events were noted. When anticoagulation prophylaxis and exclusion of patients with a history of thrombosis were implemented, thrombotic complications became uncommon.
Conclusion Monitoring of blood counts and for evidence of thromboembolic events is essential for patients treated with lenalidomide. Ongoing trials of lenalidomide combination therapy offer a treatment option for patients with advanced cancer and will better define the role of lenalidomide in solid tumors.

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Keywords Lenalidomide · Cancer · Response · Neuroendocrine · Thrombosis

Abbreviations

AEs	Adverse events
AIPC	Androgen independent prostate cancer
ASA	Aspirin
BRPC	Biochemically relapsed prostate cancer
CNS	Central nervous system
CR	Complete response
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
PD	Disease progression
PFS	Progression-free survival
PR	Partial response
PSA	Prostate-specific antigen
RECIST	Response evaluation criteria in solid tumors
SD	Stable disease
TTP	Time to progression

Introduction

Lenalidomide (CC-5013, Revlimid®, Celgene Corporation, Summit, NJ), a derivative of thalidomide, is an immunomodulatory compound (IMiD) with antiangiogenic properties. In addition to its antiangiogenic properties, lenalidomide shows immunomodulatory and anti-inflammatory effects, which apparently contribute to its antitumor activity [1]. Lenalidomide has demonstrated higher potency than thalidomide in HUVEC (human umbilical vein endothelial cells) proliferation and tube formation assays [2]. In addition to being 50,000-fold more potent at

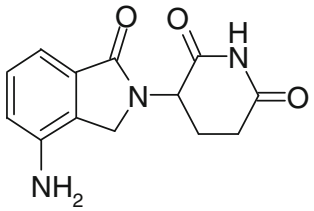

Fig. 1 Chemical structure of lenalidomide: 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

tumor necrosis factor (TNF)-alpha inhibition, this second-generation IMiD is more potent than thalidomide in co-stimulating T cells [3].

In 2005, the U.S. FDA granted Subpart H approval (restricted distribution) for lenalidomide use in patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional abnormalities. In 2006, the FDA granted approval for the use of lenalidomide combined with dexamethasone in patients with multiple myeloma who have received one prior therapy.

Chemistry

Lenalidomide is 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione (Fig. 1) (empirical formula, $C_{13}H_{13}N_3O_3$; gram molecular weight is 259.3; off-white to pale yellow solid powder, soluble in organic solvent/water mixtures and buffered aqueous solvents). Solubility was lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom, can exist as the optically active forms S(−) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

Pharmacokinetics

Lenalidomide is available commercially, in the form of Revlimid®, through a special restricted FDA-approved program (RevAssist®). Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration, with maximum plasma concentrations occurring between 0.625 and 1.5 h post-dose. Co-administration with food does not alter the extent of absorption (area under the curve [AUC]) but reduces the maximal plasma concentration (Cmax) by 36 %. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with dose increase. Multiple dosing does not result in drug accumulation.

In vitro (^{14}C)-lenalidomide binding to plasma proteins is 30 %. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. Half-life of elimination is approximately 3 h. Lenalidomide is stable at room temperature, away from sunlight and protected from excessive heat and cold.

Adverse events

Adverse events include: cytopenia, abdominal pain, nausea, vomiting, diarrhea, rash, infections, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, and thrombotic events.

Mechanisms of action

The exact mechanism of action is unclear. Lenalidomide has been shown to modulate the immune system by altering cytokine production, regulating T-cell co-stimulation, and augmenting natural killer (NK)-cell cytotoxicity.

Altering cytokine production

Lenalidomide has complex activities that affect immune regulatory function both by enhancing the activity of immune cells and inhibiting the inflammatory response by inhibiting the production of the pro-inflammatory cytokines TNF-α, IL-1β, IL-1, IL-6, IL-12, and granulocyte macrophage-colony stimulating factor (GM-CSF) and elevating the production of the anti-inflammatory cytokine IL-10 [4]. Downregulation of TNF-α secretion is particularly striking [3]. The precise mechanism of TNF-α downregulation by lenalidomide is unknown; however, thalidomide has been shown to increase the degradation of TNF-α mRNA [5, 6]. It is possible that lenalidomide may work similarly.

T-cell activation

Solid tumors produce immunologic suppressive factors that prevent priming and activation of CD4+ and CD8+ T cells of the lymph nodes [4]. Lenalidomide has been shown to stimulate both cytotoxic CD4+ and helper CD8+ cells and is significantly more potent than thalidomide as a T-cell co-stimulatory factor [7, 8].

The IMiDs have potent T-cell co-stimulatory activity, providing the second signal to T cells that have been partially activated by the T-cell receptor (TCR). For T-cell activation, not only the presentation of the peptide fragments displayed by antigen-presenting cells (APCs) to T-cell receptors (TCR) but also the interaction of B7 molecules with APC and CD28 on the T-cell surface is

necessary. The latter interaction provides the co-stimulatory signal that augments the T-cell response, aids in T-cell proliferation, differentiation, and survival, and is followed by a cascade of cytokine and cellular responses. IMiDs, including lenalidomide, act on T cells via the B7-CD28 co-stimulating pathway [9]. Downstream consequences of T-cell co-stimulation include increased levels of the secretion cytokines IFN-γ and IL-2 that, in turn, stimulate clonal T-cell proliferation and NK cell activity [4, 10, 11]. This co-stimulation is thought to overcome T-cell unresponsiveness and prevent the release of suppression factors, thereby enabling tumor-specific cells to kill tumor cells [4, 12, 13].

Augmentation of NK cell function

NK cells quickly attack the target cell and kill it with antibody-dependent cell-mediated cytotoxicity (ADCC) and natural cytotoxicity. NK cells also contribute to immunoregulation by secreting the cytokines INF-γ and TNF-α [14].

ADCC can be described as the specific lysis of cells. Lenalidomide increases the specific lysis of trastuzumab-coated breast cancer cells expressing HER-2 (SKBR3; MCF-7), cetuximab-coated colorectal cancer cells positive for EGFR expression (HCT-116; HT-29), and a variety of cell lines from various tumor types. The cell killing was increased in a dose-dependent manner, and the presence of IL-2 and IL-12 was required to achieve cell killing [15–17].

Lenalidomide enhanced ADCC in cetuximab-coated colorectal cancer cell lines with expression of EGFR (>60 %) but not in the Colo-320DM cell line with low (5 %) EGFR expression [17]. Lenalidomide enhancement of ADCC occurred in the presence of both wild-type and mutated *KRAS* and *BRAF*. EGFR expression was not associated with *KRAS* or *BRAF* mutational status. Therefore, EGFR expression is important for ADCC of cetuximab-coated colorectal cancer cells, and lenalidomide enhancement of ADCC cannot overcome this dependence. It also appears that lenalidomide enhancement of ADCC is independent of colorectal cancer *KRAS* and *BRAF* mutational status. Enhancement of ADCC by lenalidomide was unaffected by the NK cell FcγRIIIa genotype [17].

Colorectal cancer cell line expression of the NK cell ligands PVR (anti-CD0155), MIC-A, ULBP2, and ULBP3 correlated with sensitivity to ADCC [15]. NK-cell expression of NKG2D and DNAM-1 and tumor cell expression of PVR (anti-CD-155) and MIC-A correlated with the extent of ADCC and its enhancement by lenalidomide. Lenalidomide enhances the ability of IgG1-isotype antibodies to mediate the ADCC of solid tumor cells, the extent of which is largely dependent on NKG2D/NKG2D ligand interaction but appears to be independent of MIC-A/B [15, 17].

Lenalidomide-treated NK cells produced elevated levels of GM-CSF, TNF-α immune cell-recruiting chemokines (e.g., RANTES), monocyte chemotactic protein-1, IL-8, macrophage inflammatory protein (MIP)-1α, and MIP-1β in response to trastuzumab-coated SK-BR-3 tumor cells [17]. Lenalidomide enhanced the production of NK cell-derived inflammatory cytokines and chemokines in response to trastuzumab-coated SK-BR-3 breast cancer cells in vitro [17].

Antiangiogenesis

Lenalidomide was found to have 2–3 times more potent antiangiogenic activity than thalidomide in various in vivo assays [13]. Lenalidomide may affect angiogenesis through multiple mechanisms. Hypoxia, the main stimulus for angiogenesis, occurs via the induction of hypoxia-inducible factor (HIF)-1α, with subsequent activation of essential factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b-FGF) [18–20]. These growth factors stimulate capillary growth into the tumor, supplying oxygen and essential nutrients that allow the tumor mass to proliferate. Lenalidomide inhibits the pro-invasive hypoxic response in multiple tumor lines and may exert antimetastatic effects within the hypoxic solid tumor microenvironment [21]. Lenalidomide significantly inhibits hypoxia-induced HIF-1-alpha protein levels in a dose-dependent manner in many tumor cell lines, including MDA-MB-231 and MCF-7 breast cancer cell lines; HCT-116, HCT-15, and HT-29 colorectal cancer cell lines; OVCAR-3 and SKOV-3 ovarian cancer cell lines; 786-O and HEK293 renal cancer cell lines; DU-145 prostate cancer cell lines; and MiaPaca-3 pancreatic cancer cell lines [21]. Lenalidomide inhibits the hypoxia-induced mRNA expression of HIF-1-α, a key regulator of metastasis [22].

Lenalidomide inhibits growth factor-induced antiangiogenesis in vivo and is a potent inhibitor of b-FGF, VEGF, and TNF-α-induced endothelial cell migration [23]. Lenalidomide inhibits endothelial cell migration, but not proliferation [11]. The antiangiogenic activity of lenalidomide appears to be independent of immunomodulatory effects; it was not related to inhibition of endothelial cell proliferation or the ability to inhibit TNF-α or phosphodiesterase type 4 [11]. Evidence of lenalidomide's inhibition of the secretion of VEGF and bFGF by tumor and stromal cells was shown in co-culture models of multiple myeloma [24].

Lenalidomide inhibits VEGF-induced endothelial cell (HUVEC) cord formation in a dose-dependent manner, associated with inhibition of the adherens junction proteins cadherin 5, β-catenin, and CD31, and inhibition of Akt-1 phosphorylation [25].

The ability of endothelial cells to form tubes depends on the interactions of adherens junction proteins [26, 27]. In endothelial cells, cadherin 5 and CD31 connect to β-catenin, which is linked to F-actin as part of the adherens junction complex [28]. Lenalidomide inhibits the association of these proteins (cadherin 5 with β-catenin, cadherin 5 with CD31, and β-catenin with CD31) [25].

Activation of Akt plays an essential role in fundamental cellular functions such as cell proliferation and survival by phosphorylating a variety of substrates [29]. Analyses of signal transduction events show that lenalidomide partially inhibits Akt phosphorylation after VEGF stimulation in endothelial cells and has inhibitory effects on the phosphorylation of Gab1, a protein upstream of Akt 1 [23, 30].

Clinical studies

Clinical trials have shown that lenalidomide has antitumor activity in several tumor types, including prostate, thyroid, hepatocellular, and renal cell cancer.

Malignant melanoma

The antimetastatic activity of lenalidomide in vivo was evidenced in a mouse model inoculated with the mouse melanoma cell line B16-F10 [25]. Treatment with lenalidomide led to a >40 % reduction in melanoma lung metastases colony counts compared with untreated mice [25].

A phase I study demonstrated that single-agent lenalidomide was tolerable at maximal doses ≤40 mg/day [31, 32], with doses ≥75 mg/day causing unacceptable myelosuppression [33] (Table 1).

A phase II/III multicenter, randomized study comparing lenalidomide at 25 mg/day for 21 of 28 days (Arm A) to 5 mg/day continuous dosing (Arm B) in 294 patients with advanced metastatic melanoma did not show differences in overall response rates between treatment arms (Arm A, 3.4 %; Arm B, 5.5 %; $p = 0.38$) [34].

In another phase II/III multicenter, randomized study, lenalidomide at 25 mg/day on days 1–21 of a 28-day cycle was compared with placebo in patients with stage IV refractory metastatic melanoma [35]. In 128 lenalidomide-treated patients, no differences in overall response rate, survival, or time to progression were noted between patients who received lenalidomide vs. placebo ($p = 0.82$) [35].

A phase I study involving lenalidomide at 25 mg/day on days 1–14 every 21 days in combination with dacarbazine at 3 different dose levels (600, 800, and 1,000 mg/m^2) for stage III/IV melanoma in 28 patients resulted in 2 patients with complete responses, 4 with partial response [36], and 5 with stable disease [36]. The median survival was 10.6 months. Grade 3–4 adverse events occurred in 43 % of patients and included anemia, neutropenia, depression, constipation, pulmonary embolism, and cerebral ischemia [36] (Table 2).

Two phase I studies determined the maximum tolerated dose (MTD) of lenalidomide in combination with docetaxel for patients with advanced solid tumors, including 5 patients with melanoma [37, 38]. No responses were observed.

Thyroid cancer

A phase II study of lenalidomide monotherapy in follicular, papillary, insular, or Hürthle-cell metastatic thyroid carcinoma unresponsive to systemic radioiodine demonstrated a 39 % PR rate [39]. Histologies included papillary, classic ($n = 9$); tall cell variant ($n = 3$); follicular, classic ($n = 3$); and Hüthle-cell ($n = 3$). Of 18 evaluable patients, 7 (39 %) achieved a PR. The median survival for responders was 13 months. Grade 3–4 adverse events included neutropenia (44 %), leukopenia (28 %), thrombocytopenia (17 %), pulmonary embolism (11 %; patients were receiving aspirin, 81 mg/day), anemia, idiopathic and thrombocytopenic purpura, rash, anorexia, weight loss, and pneumonia (6 % each) [39].

In a phase I study of lenalidomide on days 1–14 along with docetaxel at 75 mg/m^2 on day 1 of a 21-day cycle, 33 patients (≤1 prior cytotoxic regimen) with advanced solid tumors, including 1 patient with thyroid cancer, were enrolled [37]. Lenalidomide was initiated at 5 mg/day, and the dose was increased by 5 mg per dosing cohort. Pegfilgrastin at 6 mg was added on day 2 of each cycle after 64 % of the initial 11 evaluable patients experienced grade 3–4 neutropenia. One patient (small-cell lung cancer) achieved a PR, and 20 had SD lasting 9–36 weeks. The maximum-tolerated combination dose was lenalidomide at 25 mg/day for 14 days of a 21-day cycle and docetaxel at 75 mg/m^2 once every 3 weeks. Dose-limiting toxicities (2 patients) included neutropenia, nausea/vomiting, and dyspnea [37].

Pancreatic cancer

Two patients with pancreatic adenocarcinoma had PD after 4 weeks' therapy in a phase I study of lenalidomide in 20 patients with metastatic melanoma or advanced solid tumors [32]. One patient with pancreatic cancer experienced grade 2 jaundice.

Overall, in phase I studies of single-agent lenalidomide in patients with pancreatic cancer, no responses were noted [32, 33, 40].

A phase II study evaluated lenalidomide (25 mg, days 1–21) combined with gemcitabine (1,000 mg/m^2, days 1, 8,

Table 1 Selected phase I clinical trials of lenalidomide as a single agent

Investigator [References]	Disease	Number of patients	Study design/dose, duration of lenalidomide	Response	Safety/tolerability
Sharma et al. [33]	Malignant chemotherapy-refractive tumors	55	Phase I, open-label Dose: 25–150 mg	RECIST criteria CR = 1 PR = 3 SD = 8	AEs Most common = neutropenia ($n = 8$) Grade 3/4 = 47
Bartlett et al. [32]	Metastatic malignant melanoma and other advanced cancers	20	Phase I, open-label, intrapatient dose escalation Dose: 5–50 mg/day	Stage IV melanoma ($n = 13$) PR = 1 SD = 6 PD = 6 MTD: 50 mg: 12 10 mg: 1	Grade 1–2 AEs in 87 % of pts Grade 2 AEs in 8 % Grade 4 AEs in 5 %
Tohnya et al. [31]	Refractory metastatic cancer	45	Phase I Dose: 5–40 mg	Not reported	AEs Grade 3 = 5 Grade 4 = 4
Dahut et al. [51]	Refractory solid tumors or lymphoma	45	Phase I, open-label, single center Dose: 5–40 mg	SD = 12	AEs Continuous dosing: Grade 3 = 6 Intermittent dosing: Grade 3/4 = 14
Zhang et al. [43]	Recurrent ovarian and primary peritoneal cancer	20	Phase I Dose: 25 mg/day	SD = 9 (82 %) Median TTP = 5.8 months (range, 2–12 months)	AEs Grade 3 = 13
Miller et al. [40]	Solid tumors refractory to standard treatment	20	Phase I Dose: 5–25 mg/day	PR = 1 SD = 3	AEs Grade 3 = 3
Fine et al. [63]	Recurrent primary central nervous system tumors	36 (28 evaluable)	Phase I Dose: 2.5–20 mg/m^2/day	Not reported	AEs Grade 3 = 1
Warren et al. [62]	Recurrent, refractory, or progressive primary CNS tumors	51	Phase I Dose: 15–116 mg/m^2	$N = 47$ evaluable PR = 2 SD = 23	$N = 49$ evaluable Grade 3 = 9 Grade 4 = 2

and 15) in 28-day treatment cycles to treat 72 patients with previously untreated pancreatic adenocarcinoma [41]. Patients received prophylactic anticoagulation therapy with aspirin, low-molecular-weight heparin, or warfarin. Of 72 patients enrolled, eight (11 %) achieved a PR. Progression-free survival and survival were 2.5 and 4.7 months, respectively. The 6-month survival rate was 38 %. Grade 3–4 adverse events included thrombocytopenia ($n = 15$, 21 %), neutropenia ($n = 12$, 17 %), and venous thromboembolic events ($n = 13$, 18 %). Hematologic toxicity led to dose reductions of gemcitabine and lenalidomide in 33 (46 %) and 27 (38 %) patients, respectively. Other adverse events included fatigue (49 %), nausea (33 %), anorexia (21 %), constipation (19 %), and rash (19 %) [41].

In a case report, a patient with metastatic pancreatic adenocarcinoma was treated with weekly gemcitabine (1,000 mg/m^2) [42]. When the pancreatic tumor marker

Table 2 Selected phase I clinical trials of lenalidomide combination therapy

Investigator [References]	Disease	Number of patients	Study design/dose, duration	Response	Adverse events
Hwu et al. [36]	Metastatic melanoma, stage III/IV, no prior systemic chemotherapy	28	Phase I Lenalidomide: 25 mg/day DTIC: 600, 800, and 1,000 mg/m^2	$N = 27$ evaluable ORR = 6 CR = 2 PR = 4 SD = 5 PD = 16 NE = 1 Overall survival rate: 1 year: 43 % 2 year: 21 %	Grade 3/4 = 9
Papadopoulos et al. [38]	Advanced solid tumors	30	Phase I Lenalidomide: 5–25 mg Docetaxel: 28–35 mg/m^2	Overall responses: PR = 2 SD = 8 PD = 12 Not evaluable = 8 AIPC response: 3/4 PR (RECIST) = 1 >50 % PSA↓ = 3	Grade 4 = 2 Grade 3 = 1
Sanborn et al. [37]	Advanced solid tumors	33	Phase I Lenalidomide: 25 mg/day Docetaxel: 75 mg/m^2 Dexamethasone: 4 mg	$N = 29$ evaluable PR = 1 (3.4 %) SD = 20 (69 %) Prostate pts ($n = 9$): SD = 5 PD = 2 Not evaluable = 2	$N = 32$ evaluable Grade 3–4 Prior to pegfilgrastim: 7/11 (64 %)

Table 2 continued

Investigator [References]	Disease	Number of patients	Study design/dose, duration	Response	Adverse events
Petrylak et al. [53]	Castration-resistant prostate cancer	34	Phase I, open-label Lenalidomide: 10–30 mg Docetaxel: 60 or 75 mg/m^2 Prednisone: 5 mg Dexamethasone: 8 mg	PSA response ($n = 34$): PSA $\geq$ 50 %↓: 15 (44.1 %) PSA $\geq$30 %↓: 7 (20.6 %) TTP: 200 days (range, 21–490 days) Best response measurable disease ($n = 23$) CR = 1 PR = 5 DS = 12 PD = 5	Grade 3 = 9
Mathew et al. [54]	Castration-resistant prostate cancer	10	Phase I, modular Lenalidomide: 5–25 mg Paclitaxel: 80–100 mg/m^2 ASA: 81 mg Warfarin: 2 mg	$N = 9$ evaluable 50 % PSA↓: 2 Median PFS: 13 weeks (range, 8–35 weeks) Median OS: 28 weeks (range 13–52 weeks)	Lenalidomide only: Grade 3 = 2 DLTs: Grade 3 = 6 Lenalidomide 5 mg/ Paclitaxel: Grade 3 = 3 Grade 4 = 1
Garcia et al. [55]	Progressive asymptomatic hormone-refractory prostate cancer	16	Phase I/II Lenalidomide: 25 mg	RECIST PR = 2 PSA decline: 9 (56 %)	Grade 4 = 1
Carter et al. [44]	Ovarian cancer, stage III		Phase I Lenalidomide: 5–25 mg/day Topotecan: 1.25 mg/m	Study was terminated due to toxicities	Grade 4 = 44 Grade 3 = 3
Carter et al. [45]	Recurrent epithelial ovarian cancer	11	Phase I Lenalidomide: 10, 15, 20, 25, 30 mg Liposomal doxorubicin: 40 mg/m^2		Grade 3–4 = 4

carbohydrate antigen (CA) 19-9 was increasing after 2 months, daily lenalidomide at 20 mg was administered in combination with gemcitabine given every other week. The addition of lenalidomide resulted in a decrease in the CA 19-9 level lasting for >33 months [42].

Ovarian cancer

In a phase I study of lenalidomide in recurrent ovarian primary peritoneal carcinoma, 20 patients (median number of prior therapies, 5) with advanced disease were treated [43]. Lenalidomide was administered at 25 mg/day for 21 days of a 28-day cycle. No response was seen in 11 evaluable patients. Disease stabilization for ≥3 months occurred in nine patients (82 %), including four with SD for >6 months. Ten patients had stabilization of disease or a decrease in CA-125 levels for ≥3 months (mean time to disease progression, 5.8 months) [43].

A phase I study of lenalidomide combined with topotecan terminated early because of toxicity [44]. A phase I study of lenalidomide combined with liposomal doxorubicin [45] and two other studies of lenalidomide combined with docetaxel reported no response [38, 46].

Hepatocellular cancer

In a phase II study of lenalidomide in advanced hepatocellular cancer not amenable to curative surgical resection or radio-frequency ablation, 30 patients were enrolled [47]. Five (17 %) patients achieved a PR. Six of 20 patients with elevated alpha-fetoprotein (AFP) at baseline had a ≥50 % reduction in AFP and radiographically SD. Three (10 %) patients had a long-term response (27, 24, and 13 months, respectively). The median survival was 6 months (25 % of patients, survival 25–30 months). Seventeen patients experienced ≥grade 3 adverse events [47].

In a case study, a 33-year-old man with metastatic epithelioid hemangioendothelioma was treated with lenalidomide at 25 mg daily (21/28 days) for nine cycles and 30 mg daily for another six cycles [48]. Slight regression in the lung and overall SD were observed. The splenic lesion disappeared completely [48].

Prostate cancer

Lenalidomide combined with docetaxel shows synergistic effects in in vitro and in vivo models of prostate cancer [49]. Apoptosis in lenalidomide-/docetaxel-treated prostate carcinoma cells (PC3, LNCaP, DU145) was increased compared with single-agent docetaxel. Lenalidomide restored docetaxel sensivity to the docetaxel-resistant PC3 cell line [49].

The treatment of men with biochemically recurrent prostate cancer with lenalidomide was associated with changes in circulating levels of the T(H) 2 cytokines IL-4, IL-5, IL-10, and IL-13 and global changes in immunoreactivity to a number of prostate-associated antigens [50]. Disease progression in treated patients was associated with an increase in circulating IL-8 levels, while IL-8 levels decreased in patients with non-progressive disease. Serum IL-8 levels may serve as a potential biomarker in treated patients [50].

In a phase I study of single-agent lenalidomide in 35 patients with refractory cancer [51], 9 patients had SD. Adverse events included neutropenia and thrombocytopenia.

In a phase I/II study of lenalidomide monotherapy in patients with biochemically relapsed prostate cancer at 6 months, 10 (38.5 %) of 26 treated with lenalidomide at 5 mg and 13 (38.2 %) of 34 receiving lenalidomide at 25 mg showed disease progression. Adverse events included ≥grade 3 neutropenia (15 %), thromboembolism (6 %), and skin toxicity (6 %) [51].

A phase II study of lenalidomide administered at 25 mg daily for 21 days of a 28-day cycle in patients with chemotherapy-naïve castration-resistant prostate cancer resulted in decreased serum PSA in six (38 %) patients, with a decline of >50 % in three (19 %) patients [52]. With a median follow-up of 13 months, 90 % of patients were alive [52].

Response rates in phase I studies utilizing combination therapy with taxanes range from 0 to 26 % [37, 38, 53, 54]. Grade 3–4 adverse events included cytopenia and fatigue.

A phase I/II study of lenalidomide combined with GM-CSF in hormone-refractory prostate cancer showed a decline in PSA in 56 % (9/16) of patients, with two PRs [55]. One patient developed grade 4 pulmonary embolism [55].

Preliminary results of a phase II study in 19 evaluable patients with castrate-progressive prostate cancer demonstrated three PRs when lenalidomide was used in combination with ketoconazole [56]. Decreases in PSA were seen in 74 % of patients. Grade 3–4 adverse events included fatigue (2 patients) and congestive heart failure (1 patient) [56].

In a phase II study, lenalidomide, bevacizumab, docetaxel, and prednisone combination therapy was used in chemotherapy-naïve, metastatic castration-resistant prostate cancer [57]. Treatment consisted of docetaxel at 75 mg/m^2 and bevacizumab at 15 mg/m^2 (day 1–21), lenalidomide at 25 mg (days 1–14), and prednisone at 10 mg daily (21-day cycles). Enoxaparin prophylaxis was administered. Of 32 patients completing ≥2 treatment cycles, 29 (90.6 %) and 24 (75 %) patients achieved a decrease in PSA of ≥50 % and ≥75 %, respectively. Of 17 patients with measurable disease, one had a CR, 13 had PRs, and three had SD (overall response rate, 82.4 %) [57].

A phase III study of lenalidomide combined with docetaxel and prednisone is currently recruiting patients with castrate-resistant prostate cancer. Patients will receive either lenalidomide or placebo (Table 3).

Table 3 Selected phase II/III clinical trials of lenalidomide

Investigator [References]	Disease	Number of patients	Study design/dose, duration	Response	Adverse events
Eisen et al. [35]	Stage IV metastatic malignant melanoma	306	Phase II	Lenalidomide ($N = 152$)/ Placebo ($N = 154$)	Grade 3–4
			Lenalidomide: 25 mg/day versus Placebo	ORR = 8/9	(Lenalidomide/ Placebo)
				CR = 0/1	Neutropenia = 9/2
				PR = 8/8	Leukopenia = 5/2
				SD = 65/51	Nausea = 12/15
				PD = 55/67	Constipation = 10/2
				OS: 5.9 months (range, 5.1–7.7 months)/ 7.4 months (range, 5.5–8.2 months)	Diarrhea = 9/2
				TTP: 3.0/2.1 months	Vomiting = 8/7
					Fatigue = 13/4
					Anorexia = 3/6
					Parasthesia = 6/0
					Rash = 6/0
Glaspy et al. [34]	Stage IV metastatic malignant melanoma	294	Phase II/III multicenter randomized, double-blind study	5/25 mg	5/25 mg
			Lenalidomide low dose: 5 mg/day versus Lenalidomide high dose: 25 mg/day	ORR = 5/8	Anemia = 12/22
				CR = 0/1	Nausea = 49/45
				PR = 5/7	Constipation = 35/34
				SD = 45/56	Diarrhea = 28/45
				PD = 80/61	Vomiting = 30/25
				OS:	Fatigue = 58/65
				7.2 months (range, 6.5–8.2 months)/ 6.8 months	Anorexia = 13/21
				TTP:	Arthralgia = 16/23
				1.9/2.2 months	Rash = 36/43
Ain et al. [39]	Metastatic thyroid carcinoma	25	Phase II	$N = 18$ evaluable	
			Lenalidomide: 25 mg/day	PR = 7	
				SD = 9	
Arkenau et al. [41]	Untreated pancreatic adenocarcinoma	72	Phase II	$N = 72$ evaluable	Grade 3–4:
			Lenalidomide: 25 mg	PR = 8	Thrombocytopenia: 15*
			Gemcitabine: 1,000 mg/m^2	PFS = 2.5 months	Neutropenia: 12*
				OS = 4.73 months	Venous thrombolytic events: 13*
					Fatigue: 35
					Nausea: 24
					Anorexia: 15
					Constipation: 14
					Rash: 14
Safran et al. [47]	Advanced hepatocellular carcinoma refractory to/ ineligible for sorafenib	30	Phase II	$N = 30$ evaluable	Grade 3 = 17
			Lenalidomide: 25 mg/day	PR = 5	Grade 4 = 2
				SD = 6	
				Months = 6 months	

Table 3 continued

Investigator [References]	Disease	Number of patients	Study design/dose, duration	Response	Adverse events
Lestingi et al. [52]	Chemotherapy-naïve castration-resistant prostate cancer	20	Phase II Lenalidomide: 25 mg/day	$N = 16$ evaluable Radiographically confirmed response: SD = 10 (63 %) PSA response ($n = 34$): PSA ↓:6(38 %) PSA > 50 %↓: 3 (19 %)	$N = 19$ evaluable Grade 3–4 = 29
Garcia et al. [56]	Chemotherapy-naïve castration-progressive prostate cancer	19	Phase II Lenalidomide: 25 mg/day Ketoconazole: 400 mg	$N = 18$ evaluable RECIST: PR = 3 SD = 1 PSA response: PSA ↓ 1–30 %: 3 30–50 %: 1 50–75 %: 3 75–90 %: 1 >90 %: 6	Grade 3 = 2 Grade 4 = 1
Huang et al. [57]	Metastatic castration-resistant prostate cancer Chemotherapy naïve	32	Phase II Bevacizumab: 15 mg/kg Docetaxel: 75 mg/m^2 Lenalidomide: 25 mg Prednisone: 10 mg daily	$N = 32$ evaluable RECIST: CR = 1 PR = 13 SD = 3 ORR = 82.4 % PSA response ($n = 34$): PSA ≥ 50 %↓: 29 (90.6 %) PSA ≥ 75 %↓: 24 (75 %)	$N = 32$ evaluable Grade 3 = 31
Amato et al. [58]	Refractory metastatic renal cell cancer	40	Phase II Lenalidomide: 25 mg/day	$N = 39$ evaluable CR = 1 PR = 3 SD = 21	$N = 40$ evaluable Grade 3 = 35 Grade 4 = 10
Choueiri et al. [59]	Metastatic renal cell cancer	28	Phase II Lenalidomide: 25 mg/day	$N = 28$ evaluable PR = 3 SD = 11	Grade 3 = 28 Grade 4 = 3
Patel et al. [60]	Metastatic renal cell cancer	14	Phase II Lenalidomide: 25 mg/day	$N = 14$ evaluable SD = 8	$N = 14$ evaluable Grade 3 = 26

Renal cell cancer

In a phase II trial, lenalidomide was administered at 25 mg daily for 21 days (28-day cycle) in patients with metastatic renal cell carcinoma [58]. Of 39 evaluable patients, 33 had a clear cell histotype and 27 had undergone previous immunotherapy or chemotherapy. A CR was observed in one (3 %) patient, a PR in 3 (8 %), and SD in 21 (53 %). Time to progression was 6 to ≥12 months. Adverse events, including ≥grade 3, were neutropenia (50 %) and thrombocytopenia (28 %) [58].

In another phase II study, lenalidomide was administered at 25 mg daily for 21 days (28-day cycle) in patients with metastatic renal cell carcinoma [59]. Of 28 patients, three (11 %) had a PR and were progression free for >15+ months; 11 (39 %) had SD lasting >3 months, including eight patients who had tumor shrinkage. Adverse events included fatigue (11 %), skin toxicity (11 %), and neutropenia (36 %) [59].

In another phase II study of lenalidomide (25 mg daily for 21 days of a 28-day cycle) in 14 patients with metastatic renal cell carcinoma, eight (57 %) patients had SD [60].

Brain cancer

In vitro studies demonstrated that lenalidomide alone or combined with ultraviolet B or photon irradiation did not have a significant effect on cell death, cell growth, or cell proliferation in glioblastoma multiforme [61].

In a phase I trial of lenalidomide in children with recurrent, refractory, or progressive primary central nervous system tumors, lenalidomide was administered daily for 21 days (every 28 days) [62]. The starting dose was 15 mg/m^2/day orally. The primary toxicity was myelosuppression. The MTD was not reached with the highest dose tested (116 mg/m^2/day). Of 51 patients, 2 had objective responses (thalmic juvenile pilocytic astrocytoma, $n = 1$; optic pathway glioma, $n = 1$). Objective response or long-term SD was observed in patients with low-grade gliomas [62].

In a phase I trial of lenalidomide in 36 patients with recurrent primary central nervous system tumors, no responses were noted [63].

In a pilot study of lenalidomide and radiotherapy for patients with newly diagnosed glioblastoma mutliforme, no responses were noted [64].

Lung cancer

In a phase I study of lenalidomide (5, 10, 25 mg/day) in 20 patients with solid tumors, one patient (25 mg/day) developed grade 3 motor neuropathy [40]. One patient with non-small-cell lung cancer (NSCLC) had a PR, and three patients had SD (NSCLC, $n = 2$; epithelioid hemangioendothelioma, $n = 1$). Responders with NSCLC had received prior gemcitabine, carboplatin, and docetaxel [40].

In a phase I study of 3-weekly docetaxel, carboplatin, and lenalidomide in patients with advanced solid tumors, 14 patients were enrolled [65]. Treatment consisted of docetaxel (60 mg/m^2), carboplatin (AUC 6) on day 1 and either 10 mg (dose level 1) or 5 mg (dose level 2) lenalidomide orally daily on days 1–14. Three of four patients treated at dose level 1 experienced dose-limiting toxicity (DLT) (grade 3 electrolyte abnormalities, $n = 2$ and grade 4 neutropenia, $n = 1$). Ten patients were treated at dose level 2, with one DLT (grade 4 neutropenia). Five patients achieved a PR (5 of 9 with NSCLC) [65].

In a phase I study, lenalidomide (days 1–14) and docetaxel at 75 mg/m^2 on day 1 (21-day cycle) were administered in 33 patients ($\leq$1 prior cytotoxic regimen) with cancer [37]. Lenalidomide was initiated at 5 mg/day and increased by 5 mg per cohort. Pegfilgrastim (6 mg) was added on day 2. One patient (small-cell lung cancer) achieved a PR, and 20 had SD (duration, 9–36 weeks). Five of nine patients with prostate cancer had SD (MTD: lenalidomide, 25 mg/day for 14 days; docetaxel, 75 mg/m^2 once every 3 weeks). Two patients experienced DLT (neutropenia, nausea, vomiting, and dyspnea) [37].

Sarcoma

Phase I studies included patients with sarcoma treated with lenalidomide alone ($n = 1$) or in combination with docetaxel ($n = 7$) [33, 46]. No antitumor activity was reported.

In a study of patients with myelodysplastic syndromes with a deletion 5q cytogenetic abnormality, an 84-year-old patient received lenalidomide and became transfusion independent [66]. One year later (March 2005), a low-grade malignant sarcoma was discovered at the lesser curvature of his stomach. Repeated computed tomography scans performed in October 2005 and December 2006 were negative for the presence of the mass. A potential therapeutic role of lenalidomide in this case is possible, although spontaneous regression cannot be excluded [66].

Breast cancer

In a vitamin D-resistant breast cancer cell line (MDA-MB-231), a 50 % inhibition of cell growth by biologically active vitamin D (*a*,25-dihydroxyvitamin D3; 1,25 D3) was achieved in the presence of lenalidomide [67]. The combination of 1,25 D3 and lenalidomide resulted in an increase in pro-apoptotic protein expression leading to inhibition of cell viability and growth [67].

Phase I studies of lenalidomide included patients with breast cancer but did not report clinical efficacy [38, 40].

Colon cancer

Lenalidomide increases the antibody-dependent cell-mediated cytotoxicity of NK cells in cetuximab-coated colorectal cancer cells positive for EGFR expression in vitro (HCT-116; HT-29) (17). In experiments with colorectal cancer cell lines (CT26, CMT93), the numbers of live colonies and migration of cells were significantly reduced after culturing with lenalidomide [68]. Metastasis was reduced in mice inoculated with colorectal cancer cells (CT26) pre-treated with lenalidomide in vivo [68].

Clinical studies included patients with colorectal cancer, but no response was reported (31, 37, 40).

Ongoing clinical trials

Over 220 clinical trials are investigating the role of lenalidomide in solid tumors. We are currently conducting a

phase I study of lenalidomide in combination with bevacizumab, sorafenib, temsirolimus, 5-fluorouracil, leucovorin, and oxaliplatin in patients with advanced cancers. To date, treatment has been well tolerated and selected patients have responded to treatment, one patient with neuroendocrine cancer had a PR after 2 cycles of treatment with lenalidomide and temsirolimus.

Conclusions

Lenalidomide was the first of the second-generation IMiD compounds to gain FDA approval for the treatment of patients with myelodysplastic syndromes and multiple myeloma. Lenalidomide has antitumor activity in a variety of solid tumors both as a single agent and in combination with cytotoxic or targeted agents. The emerging knowledge regarding the mechanism of action and results of ongoing clinical trials in various tumor types will define the antitumor activity of lenalidomide. In the era of personalized cancer therapy, future research should focus on the identification of patients who respond to lenalidomide.

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