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Edrecolomab (Monoclonal Antibody 17-1A)

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Contents

Abstract

▲ Edrecolomab is a mouse-derived monoclonal IgG2a antibody. It recognises the human tumour-associated antigen CO17-1A which is expressed on the cell surface of a wide variety of tumours and normal epithelial tissue.

▲ Edrecolomab is thought to destroy tumour cells by activating an array of endogenous cytotoxic mechanisms, including antibody-dependent cell-mediated cytotoxicity and possibly antibody-dependent complement-mediated cytotoxicity. Edrecolomab may induce antitumour activity indirectly by inducing a host anti-idiotypic antibody response.

▲ Adjuvant therapy with edrecolomab (500mg initial dose followed by four 100mg infusions administered at 4-weekly intervals) significantly improved survival and reduced the tumour recurrence rate in patients with resected Dukes' stage C colorectal cancer and minimal residual disease.

▲ Data from several small clinical trials suggest that edrecolomab given as monotherapy or in combination with other antineoplastic agents has limited efficacy in the treatment of advanced colorectal or pancreatic tumours. However, results from a small phase I study in patients with advanced breast cancer were more promising.

▲ Edrecolomab was generally well tolerated in clinical trials. In a postmarketing surveillance study, the most common adverse events associated with edrecolomab were flushing/erythema and gastrointestinal symptoms including diarrhoea, abdominal pain and nausea and vomiting. Because edrecolomab is of murine origin, anaphylactic reactions have developed in some patients treated with the drug.

Features and properties of edrecolomab (monoclonal antibody 17-1A)	
Indications	
Postoperative adjuvant therapy of colorectal carcinoma, Dukes' stage C	
Mechanism of action	
Murine monoclonal IgG2a antibody	Recognises the CO17-1A cell surface glycoprotein which is expressed on tumours and normal epithelial cells
Dosage and administration	
Dosage	500mg administered ≤6 weeks (preferably ≤2 weeks) after surgery; 4 additional single doses of 100mg are then administered at 4-weekly intervals
Route of administration	Intravenous infusion administered over 2 hours in 250ml of sodium chloride 0.9%
Pharmacokinetic profile (after single-dose intravenous administration of 500mg)	
Maximum plasma concentration	100-132 mg/L
Area under the plasma concentration-time curve	2454-4975 mg/L • h
Total body clearance	0.21 L/h
Volume of distribution	5.1L
Elimination half-life	19.8h
Adverse events	
Most frequent	Diarrhoea, abdominal pain, nausea and vomiting, flushing/erythema and anaphylaxis (infrequent)

Edrecolomab is a mouse-derived monoclonal IgG2a antibody which recognises the human tumour-associated antigen CO17-1A. CO17-1A is expressed on the cell surface of a wide variety of tumours including carcinomas of the colon, rectum, pancreas and stomach and it is also present in normal epithelial tissue.[1-4] Although monotherapy with unconjugated monoclonal antibodies has been widely investigated in the treatment of solid tumours, complete tumour regressions are infrequent.[5-7] Restricted accessibility of tumour cells has frequently been cited as one of the major reasons for the limited efficacy of monoclonal antibodies in this setting.[5-7] However, it is now becoming increasingly apparent that patients presenting with minimal residual disease or micrometastatic disease after surgical resection will benefit most from monoclonal antibody therapy. Indeed, disseminated epithelial cells in the bone marrow of patients with colorectal cancer have been shown to be independent and strong predictors of later clinical relapse.[8]

1. Pharmacodynamic Profile

- Monoclonal antibodies are thought to destroy tumour cells by activating an array of endogenous cytotoxic mechanisms including antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent complement-mediated cytotoxicity (ADCMC).[5]

- After incubation with edrecolomab, human monocytes and macrophages were capable of lysing human colorectal cancer cells in an *in vitro* assay of ADCC.[9]

- The ADCC of edrecolomab against the colorectal carcinoma cell line HT29 was significantly increased by incubation with interferon-α, interferon-γ (IFNγ) and interleukin-2 but not by granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor or tumour necrosis factor-α.[10]

- Incubation of colorectal cancer cells with a combination of edrecolomab and other noncompeting murine monoclonal antibodies resulted in ADCMC. However, like other murine monoclonal antibodies, edrecolomab was unable to generate ADCMC *in vitro* when used alone.[11]

- In addition to the preceding mechanisms, edrecolomab appears to invoke antitumour activity indirectly by inducing a host anti-idiotypic antibody response to produce anti-anti-idiotypic antibodies (ab_3) which recognise the same epitope as edrecolomab.[12-17] 78 and 95% of patients treated with multiple doses of edrecolomab produced anti-idiotypic antibodies (ab_2) in 2 studies and 47% produced ab_3 antibodies in 1 of these studies.[14,16] Notably, a survival advantage has been reported for edrecolomab-treated patients who develop ab_3 antibodies compared with those who do not.[13,14]

- Induction of a T cell-mediated immune network cascade may also be important for tumour response to edrecolomab therapy.[12,15,18]

- The development and growth of human colorectal carcinoma cells implanted into nude mice was significantly inhibited by intraperitoneal administration of edrecolomab (400 μg/day for at least 7 days starting immediately or 1 hour after innoculation with cancer cells).[19,20]

2. Pharmacokinetic Profile

- In 3 studies in patients with gastrointestinal, colorectal or pancreatic cancer, the plasma pharmacokinetic profile of edrecolomab was similar and generally described by a 1-compartment model.[21-23] However, in 1 patient a 2-compartment model best described the pharmacokinetics of the drug.[21]

- A mean maximum edrecolomab plasma concentration (C_{max}) of 100 mg/L was achieved after single-dose intravenous administration of edrecolomab 500mg to patients with pancreatic cancer (n = 5).[21] Mean area under the plasma concentration-time curve (AUC) was 2454 mg/L · h.[21]

- The pharmacokinetic profile of edrecolomab 400mg was investigated in patients with metastatic gastrointestinal adenocarcinoma administered either 1 (n = 5), 2 (n = 10) or 3 (n = 3) doses at weekly intervals or 4 doses over an 8-day period (n = 5). Mean C_{max} values were between 118 and 156 mg/L and AUC values were between 2647 and 3955

mg/L · h.[23] The pharmacokinetics of edrecolomab were similar after single- and multiple-dose administration of the drug.[23]

• In 24 patients with metastatic colorectal cancer, C_{max} which occurred at 2 hours (mean 55 to 132 mg/L) and AUC values (mean 2045 to 4975 mg/L · h) increased with increasing edrecolomab doses (200 to 500mg) but were subject to wide interindividual variation.[22] The source of edrecolomab [mouse ascitic fluid (14 patients), cell culture supernatant (7 patients) or both (3 patients)] did not significantly alter the pharmacokinetics of the drug.[24]

• Plasma elimination half-life ($t_{½\beta}$) values of edrecolomab were 14.4 to 28.6 hours after administration of edrecolomab 200 to 500mg to patients with cancer.[22,23]

• Total plasma clearance of edrecolomab ranged from 0.0019 to 0.0026 L/h/kg[23] and total body clearance was 0.21 L/h.[21] Volume of distribution values of 0.039 to 0.057 L/kg and 5.1L have been reported for edrecolomab, which suggest that the drug is confined mainly to the plasma volume and achieves minimal penetration into the interstitial space.[21,23]

• The presence of human antimouse antibodies (HAMA) in serum did not alter the pharmacokinetic profile of edrecolomab at doses >100mg.[22,23]

3. Therapeutic Trials

The efficacy of edrecolomab has been evaluated both as adjuvant therapy in patients with minimal residual disease after resection for colorectal carcinoma and in patients with advanced gastrointestinal tumours or advanced breast cancer. Overall survival and disease-free survival were the primary efficacy parameters in the trial of patients with minimal residual disease. In patients with advanced malignancies, response to therapy was generally defined as follows: complete response (CR; complete disappearance of all measurable lesions), partial response (PR; ≥50% reduction in the product of 2 perpendicular diameters of all measurable lesions), minor response (MR; 25 to 50% reduction in the product of 2 perpendicular diameters of ≥1 tumour lesion), stable disease [SD; definition varied but included no significant change (≤25% reduction) in the size of any measurable lesions for at least 3 months or failure to meet criteria for complete or partial response or progressive disease] or progressive disease (PD; generally >25% or >50% increase in the size of measurable lesions).

Edrecolomab was administered by intravenous infusion over a period of 0.5 to 2 hours; in some studies edrecolomab was admixed with autologous mononuclear cells, isolated by standard leucopheresis techniques, prior to administration.[17,25-27]

Colorectal Cancer

Minimal Residual Disease

Monotherapy

• In a multicentre randomised study, edrecolomab (500mg administered 2 weeks postoperatively followed by four 100mg infusions administered at 4-weekly intervals) was compared with observation alone in 166 eligible patients with Dukes' stage C colorectal cancer who had undergone curative surgery and were free of manifest residual tumour (96 patients originally had colon cancer and 70 had rectal cancer).[28] After a median follow-up of 5 years, treatment with edrecolomab resulted in a relative reduction in mortality of 30% (Cox's proportional hazards model $p = 0.04$; log-rank test $p = 0.05$) and a relative reduction in tumour recurrence rate of 27% ($p = 0.03$, $p = 0.05$) compared with observation alone. Edrecolomab had no effect on the incidence of local relapses; however, distant recurrences as a first sign of relapse were significantly reduced ($p = 0.0014$, $p = 0.002$).[28]

• After a median follow-up of 7 years in the above study, edrecolomab was associated with a relative reduction in mortality of 32% (Cox's proportional hazards model $p < 0.01$; log-rank test $p = 0.01$) [fig. 1] and a relative reduction in tumour recurrence rate of 23% compared with observation alone (hazards ratio 0.66; 95% confidence interval 1 to 43%).[29] The incidence of distant metastatic recurrences was significantly reduced among patients

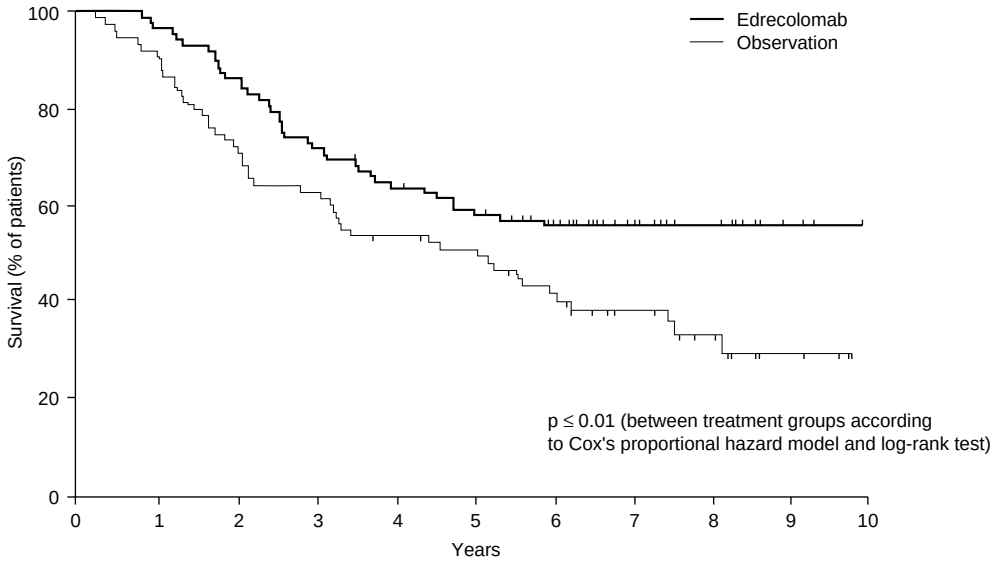

Fig. 1. Clinical efficacy of edrecolomab. Seven-year overall survival for eligible patients randomised to treatment with edrecolomab (n = 90; 500mg followed by four 100mg infusions administered at 4-weekly intervals) or observation alone (n = 76) after undergoing curative surgery for Dukes' stage C colorectal cancer (from Riethmüller et al.,[29] with permission).

treated with edrecolomab (p = 0.004 *vs* observation alone), whereas local relapses were not.

- A large phase III North American intergroup study is currently comparing edrecolomab as postoperative adjuvant therapy (500mg administered 2 to 6 weeks after curative resection followed by 4 infusions of 100mg administered at 4-weekly intervals) with no treatment in patients with high risk Dukes' stage B colon cancer.[30] A European multicentre trial of a similar design is also under way.[31]

Combination Therapy

- Whether the efficacy of edrecolomab can be increased by combination with an antineoplastic agent is currently being assessed in 3 large phase III studies.[30] Two studies are in patients with resected Duke's stage C colon cancer. One study is comparing treatment with fluorouracil-based chemotherapy (fluorouracil plus levamisole or leucovorin) alone and in combination with edrecolomab. The second study has 3 treatment arms comparing edrecolomab alone, edrecolomab plus fluorouracil/leucovorin and fluorouracil/leucovorin alone. A third study is comparing adjuvant treatment with edrecolomab plus fluorouracil/leucovorin with fluorouracil/leucovorin alone in patients with Dukes' stage B or C rectal cancer who received preoperative radiotherapy.

Advanced Disease

Monotherapy

- 71 patients with inoperable metastatic colorectal cancer were treated with varying edrecolomab dosage schedules (total dose 1 to 12g over a period of approximately ≤1 year).[25] Six patients had previously received chemotherapy and 5 others had received radiotherapy. All other patients were previously untreated except for primary surgery. One patient achieved a PR and a survival duration of >114 months and 10 patients achieved a MR or SD for ≥3 months. The median response duration for all 11 patients was 7.4 months. The response rate tended to decrease with increasing dose intensity; the overall response rate was 22% (1 PR, 3 MR and 6 SD) for 45 patients treated with a total dose of edrecolomab <2g, whereas the corresponding response rate for patients treated with edrecolomab >2g was 4% (1 SD) [p < 0.05 between

groups]. Although overall survival was 11 months, responding patients survived significantly longer than nonresponding patients (median survival 20 *vs* 10 months; p = 0.0027).

Combination Therapy

- Single-dose edrecolomab (400mg on day 3 of cycle) plus GM-CSF [250 μg/m^2/day subcutaneously for 10 days] was evaluated in 20 patients with metastatic colorectal cancer. The treatment cycle was repeated every 4 weeks and 4 cycles were administered. All patients had previously undergone surgery and 2 patients had also previously received chemotherapy with or without radiotherapy. Two patients achieved a CR of >23 and >29 months' duration and 1 patient achieved a MR; a further 3 patients had SD for >3 months.[32]

- 15 of 22 patients (68%) with advanced colorectal cancer experienced no change and 4 patients had SD after treatment with edrecolomab 400mg followed by 4-weekly treatment with edrecolomab 100mg plus fluorouracil-based chemotherapy.[33] Major symptomatic improvement was reported in 2 patients who were previously refractory to standard fluorouracil-based chemotherapy. One patient was omitted from the efficacy assessment.

- In a phase II study of IFNγ (0.1 mg/m^2 on days 1 to 15) plus edrecolomab (400mg on days 5, 7, 9 and 12), SD was observed in 3 of 14 evaluable patients at 8 weeks and PD occurred in 11 patients with metastatic colorectal cancer. Median survival was 56 weeks. 11 of the 15 patients had previously been treated with chemotherapy and/or radiotherapy.[34]

- In another phase II study, 17 of 18 evaluable patients (≈12 previously treated with chemotherapy and/or radiotherapy) experienced PD within 2 months of treatment with edrecolomab 150mg (days 2, 3 and 4) plus IFNγ (1.0×10^6 IU/m^2 on days 1 to 4).[35] One patient had SD for 2 months at the time of the study report.

Advanced Pancreatic Cancer

Monotherapy

- In 2 preliminary phase II studies, a total of 42 patients with advanced pancreatic cancer were treated with a single dose of edrecolomab 400mg; an additional patient received 3 separate doses of edrecolomab 400mg. 16 patients had received prior chemotherapy and/or radiotherapy. PRs were reported in 4 evaluable patients, 9 patients had SD and PD was observed in 30 patients.[17,26]

- In a subsequent phase II study, 22 evaluable patients with unresectable pancreatic cancer were treated with edrecolomab 500mg 3 times weekly for 8 weeks (prior therapy: radiotherapy and/or chemotherapy n = 12; surgery n= 7).[21] One patient achieved a sustained PR for >3 years. Six patients developed symptomatic early PD necessitating cessation of therapy. At the end of therapy, 5 patients demonstrated brief periods of SD and 10 patients had PD. Mean progression-free survival was 50 days and mean overall survival for all treated patients (n = 28) was 82 days from the first infusion of antibody.

Combination Therapy

- Combination therapy with edrecolomab 150mg (on days 2, 3 and 4) plus IFNγ 1.0×10^6 IU/m^2 (on days 1 to 4) resulted in a CR of 4 months' duration in 1 of 25 evaluable patients with advanced pancreatic cancer (prior chemotherapy or radiotherapy n = 7); 9 further patients had SD for ≥2 months.[27] Overall median survival was 5 months in this phase II study.

- Edrecolomab 400mg plus fluorouracil, doxorubicin and mitomycin chemotherapy produced PRs of 7 and 11 months' duration in 2 of 8 previously untreated patients with advanced pancreatic cancer.[36]

Advanced Breast Cancer

- In a small phase I study, patients with stage II/III breast cancer involving ≥10 axillary lymph nodes (n = 6) or stage IV breast cancer (n = 4) were treated with high-dose chemotherapy followed by transplantation of tumour-cell-purged peripheral blood stem cell grafts.[37] The patients then received edrecolomab 500mg followed by 4 doses of edrecolomab 100mg administered at 4-weekly intervals. After a median follow-up of 20 months, 8 patients

had achieved a CR, 1 patient had a PR and 1 patient developed PD and died.

4. Tolerability

- In clinical trials, adverse events associated with edrecolomab therapy were generally mild or moderate and reversible on discontinuation of treatment. Because edrecolomab is of murine origin, anaphylactic reactions have developed in some patients treated with the drug.

- In a dose-ranging study (total edrecolomab dose 1 to 12g over approximately ≤1 year), adverse events associated with edrecolomab therapy were of short duration. Diarrhoea was the most frequent adverse event; it resolved within 24 hours and was more frequent at higher edrecolomab doses (400 or 500mg).[25] Five of 67 patients became hypotensive after receiving 3 edrecolomab infusions (dose and time interval not specified); however, their blood pressure normalised within 15 minutes of administration of hydrocortisone.

- In a randomised study, 31 of 83 patients with Dukes' stage C colorectal cancer treated with edrecolomab (total dose 900mg) developed a total of 45 adverse events.[28] The majority of adverse events were reported during the first treatment cycle and most frequently included diarrhoea (7 events), flushing/rash (7), fever/chills (4), malaise/dizziness/fatigue (4), nausea and/or vomiting (4), abdominal cramps (3) and unspecified cardiovascular effects (3). Four cases of anaphylaxis were reported and these were successfully controlled within 1 hour of onset with intravenous hydrocortisone.

- In a postmarketing surveillance study, 135 of 277 patients (48.7%) treated with edrecolomab (dose not specified) as adjuvant therapy for stage I to IV colorectal cancer developed adverse events (WHO grade 1 to 4); diarrhoea (30.7% of patients), nausea (20.2%), abdominal pain (18.7%), flushing/erythema (8.3%), vomiting (7.9%) and anaphylactic reaction (2.9%) were the most frequently reported adverse events (fig. 2).[38] 32 patients (11.6%) developed WHO grade 3 or 4 adverse events which necessitated discontinuation of edrecolomab therapy; these events resolved with symptomatic treat-

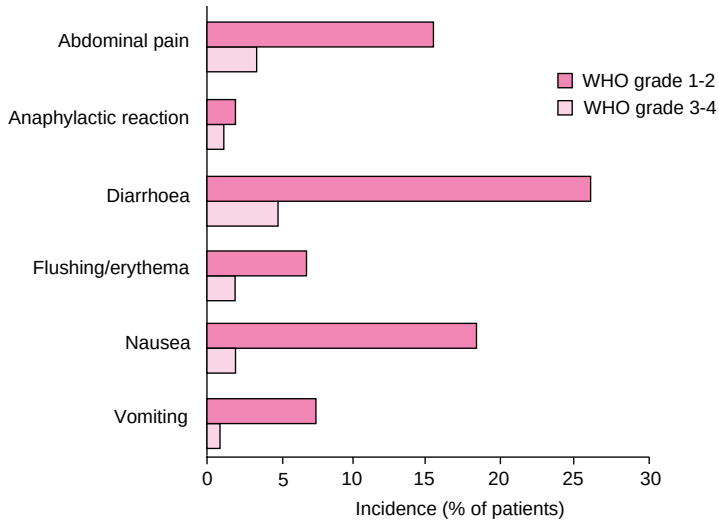

Fig. 2. Incidence of edrecolomab-associated adverse events in a postmarketing surveillance study. Incidence of WHO grade 1 to 2 or 3 to 4 adverse events in 277 patients treated for colorectal cancer with edrecolomab (dose not specified).[38]

ment and most frequently included diarrhoea (4.7%) and abdominal pain (3.2%) [fig. 2].

• Hypersensitivity reactions necessitating cessation of therapy developed in 5 of 28 patients with pancreatic cancer treated with edrecolomab (500mg 3 times weekly for 8 weeks).[21] All hypersensitivity reactions developed before the end of the 3rd week of treatment and most frequently manifested as fever, nausea and vomiting and less frequently as back pain, urticaria, hypotension or arthralgias. Retreatment of 3 patients with edrecolomab after an initial hypersensitivity reaction led to symptom recurrence; however, all hypersensitivity reactions resolved rapidly with standard medical management and without long term sequelae.

• Five per cent of patients treated for colorectal cancer with edrecolomab 400mg and GM-CSF developed an immediate-type allergic reaction (including bronchospasm, hypotension, fever and chills) during the first treatment cycle in 1 study and this increased to 18 and 78% of patients during the second and third treatment cycles, respectively.[32]

• Bronchospasm, which resolved on medical intervention, was reported after initial exposure to edrecolomab 150mg in 1 patient with a history of generalised atopy.[27]

• In a phase I study, grade 2 diarrhoea (7 patients), erythema (5), leucopenia (3) and skeletal pain (3) were reported in patients with rectal cancer stage III (n = 12) or local recurrences (n = 3) treated postoperatively with edrecolomab (total dose 900mg) plus fluorouracil-based radiochemotherapy.[39] Radiochemotherapy was continued in 2 patients in whom edrecolomab was stopped because of suspected allergy.

Human Antimouse Antibodies

• Positive HAMA titres developed in approximately 62 to 100% of patients treated with edrecolomab in clinical trials.[17,23,25,26,28,34,40,41] In a large randomised study, 80% of patients treated with edrecolomab (total dose 900mg) developed a HAMA response after the second or third infusion.[28] HAMA titres were low (≤0.6 mg/L of serum) after the first 2 infusions, reached their maximum after the 5th infusion (≤2.8 mg/L of serum) and remained detectable for 2 years after treatment.

5. Edrecolomab: Current Status

Current data suggest that edrecolomab produces greatest efficacy when used as adjuvant therapy for resected colorectal cancer. In this setting, edrecolomab has been shown to prolong survival and suppress or delay the appearance of distant metastases. Edrecolomab is currently approved in Germany as postoperative adjuvant therapy for patients with Dukes' stage C colorectal cancer.

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