Cooperation of the Agonistic DR5 Antibody Apomab with Chemotherapy to Inhibit Orthotopic Lung Tumor Growth and Improve Survival

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Abstract

Purpose: Apomab is a fully human monoclonal antibody that induces programmed cell death through the proapoptotic receptor DR5 in various cancer cells but not in normal cells. Several lung cancer cell lines express DR5 and exhibit apoptosis in response to apomab in vitro.

Experimental Design: We investigated the efficacy of apomab and its interaction with chemotherapy in xenograft models based on human NCI-H460 non–small-cell lung carcinoma cells. In an established model of s.c. tumor xenografts, apomab or Taxol plus carboplatin chemotherapy delayed tumor progression, whereas combined treatment caused tumor regression and a substantially longer growth delay. To test apomab activity in a setting that may more closely mimic lung cancer pathology in patients, we developed a lung orthotopic model.

Results: In this model, microcomputer tomography imaging showed that apomab, chemotherapy, or combination treatments significantly inhibited tumor growth compared with vehicle, whereas the combination caused greater inhibition in tumor growth relative to chemotherapy or apomab. Similarly, histologic analysis revealed that apomab, chemotherapy, or the combination significantly reduced tumor size compared with vehicle, whereas the combination induced significantly greater reduction in tumor size than did chemotherapy or apomab. Furthermore, combined treatment improved 105-day survival relative to vehicle (P = 0.0023) as well as to apomab (P = 0.00445) or chemotherapy (P = 0.0415).

Conclusion: These results show a positive interaction of apomab with chemotherapy, evidenced by significant inhibition of tumor growth as well as improved survival, thus supporting further investigation of this therapeutic approach in lung cancer patients.

Lung cancer is the most common malignancy worldwide. It has been estimated that in the United States, ~213,380 people (114,760 males and 98,620 females) will have been diagnosed with lung cancer in 2007 (1). Moreover, lung cancer is the leading cause of cancer mortality, expected to account for 30.9% of such deaths in men and 26.2% in women in the United States in 2007 (1). Approximately 80% of lung cancers are defined as non–small-cell lung cancer (NSCLC). Although there have been major improvements over recent decades in surgical techniques, chemotherapy, and radiotherapy for the treatment of NSCLC, the long-term outlook for these patients has not changed significantly (2). Therefore, there is an unmet medical need for more effective treatment of this disease.

A recent experimental approach to cancer therapy has aimed to trigger apoptosis (programmed cell death) selectively in cancer cells by targeting proapoptotic receptors (3–6). Apo2 ligand/tumor necrosis factor-related apoptosis-inducing ligand (Apo2L/TRAIL) is an apoptosis-inducing member of the tumor necrosis factor superfamily (7, 8). There are at least five receptors for Apo2L/TRAIL (9–19); two of them, DR4 (TRAIL-R1) and DR5 (TRAIL-R2), can transduce apoptosis signals (9–14), whereas the other three, DcR1 (TRAIL-R3), DcR2 (TRAIL-R4), and OPG, function as decoy receptors that block Apo2L/TRAIL-mediated apoptosis (15–19). To date, two molecular types of proapoptotic receptor agonists that target DR5 and/or DR4 have been developed. The first is recombinant human Apo2L/TRAIL (rhApo2L/TRAIL), which stimulates both DR4 and DR5 (20–23). Its compelling antitumor activity, both as a single agent and in combination with chemotherapy, has been extensively documented in various preclinical cancer models (3, 21, 23, 24). The second molecular type is represented by human agonistic antibodies that activate DR5 or DR4 (25–30). We have generated a fully human monoclonal antibody (apomab) that induces tumor cell apoptosis through DR5 while sparing normal cells including hepatocytes (31). The efficacy of agonistic antibodies to DR5 against lung tumors has been tested in vitro and in vivo; however, the analysis of in vivo activity has been primarily directed to mouse models of s.c. tumor xenografts. The activity of agonistic antibodies to DR5

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against lung tumors growing in an orthotopic pulmonary tissue setting and the effect of agonistic DR5 antibody treatment on the survival of tumor-bearing animals have not been reported in the published scientific literature.

In the present study, we tested the effect of apomab monotherapy or its combination with chemotherapy on tumor progression and host survival in a nude mouse model based on orthotopic xenografts derived from the human NSCLC cell line NCI-H460. In addition, we used a novel microcomputed tomography (microCT) imaging technique to assess lung tumor growth in each animal. Apomab exerted antitumor activity as a single agent and cooperated with clinically established chemotherapy against NSCLC in the orthotopic model, suggesting that this agent is capable of exerting activity against tumor cells growing in such a tissue microenvironment.

Materials and Methods

Cell lines and reagents. The human cell line NCI-H460 was obtained from the American Type Cell Culture Collection, and maintained in RPMI medium supplemented with 10% fetal bovine serum and 10% fetal bovine serum (Invitrogen) under conditions of 5% CO2 at 37°C. Apomab, a fully human monoclonal agonistic antibody to DR5, was produced at Genentech, Inc. (28). Goat F(ab')2 anti-human IgG Fc was purchased from Pierce. Taxol (paclitaxel) and carboplatin (para-platin) were purchased from Bristol-Myers Squibb Co.

In vitro studies. NCI-H460 NSCLC cells were plated in 96-well plates (5,000 cells per well) and incubated overnight at 37°C in RPMI 1640 with 10% fetal bovine serum. Next, medium was replaced, and the cells were incubated with apomab (1 ng/mL to 1 μg/mL) plus antihuman Fc antibody (10 μg/mL) in the absence or presence of Taxol (10 ng/mL) for 48 h. Anti-Fc antibody crosslinking was used to enhance apomab activity in vitro (31). Cell viability was determined by AlamarBlue assay (Trek Diagnostic System, Inc.).

Analysis of caspase-3/7 activity was done using the Apo-ONE Homogenous Caspase-3/7 assay (Promega). NCI-H460 cells were incubated with apomab plus antihuman Fc antibody in the absence or presence of Taxol for 24 h before lysis and addition of a fluorescent caspase substrate.
inserted through the sixth intercostal space into the lung parenchyma to a depth of 3 mm. Human NCI-H460 cells (one million), suspended in 20 μL HBSS containing Matrigel (v/v = 1/1), were injected into the lung parenchyma. After injection, a cotton-tipped applicator was pressed on the injection site to stop any bleeding, and the skin incision was closed with a surgical skin clip. Our previous study shows that this orthotopic model of lung cancer is useful for preclinical studies to test the antitumor efficacy of novel molecules (24).

MicroCT imaging of the lungs was carried out under anesthesia with isoflurane 10 d after lung parenchymal injection of tumor cells. Based on microCT measurement of tumor volume, the mice were divided into four groups with a comparable tumor volume in each group and treated with vehicle, apomab (10 mg/kg/d i.p. every 5 d for 15 d), chemotherapy (Taxol at 6.25 mg/kg/d s.c. for 5 d, plus carboplatin at 100 mg/kg, single i.p. dose), or the combination of apomab and chemotherapy. On day 25 after study initiation, the mice were again imaged by microCT and tumor volume in the lungs was assessed. Finally, the animals were anesthetized with pentobarbital sodium (60 mg/kg i.p.), and the lungs were removed and fixed in 10% buffered formalin for histologic studies.

**MicroCT imaging.** Serial lung imaging was done with an in vivo microCT system (vivaCT 40; Scanco Medical). Data were acquired at 38 μm isotropic voxel size, 1,000 projections, 250 ms integration time, 45 keV photon energy, and 177 mA current. During in vivo imaging the animals were anesthetized with 2% isoflurane in air and kept at constant 37°C temperature by regulated warm airflow. The imaging time at each time point was ~25 min per animal and the estimated radiation dose was 0.2 Gy.

Image data were evaluated with the aid of Analyze (AnalyzeDirect, Inc.), an image analysis software package. Lung tumor volume estimates were derived by viewing three orthogonal planes of the microCT data, from which estimates of maximal tumor diameter (d1), the largest perpendicular diameter (d2), and tumor diameter along the third dimension (d3) were made. The tumor volume was determined to be one half the cross-product of the tridirectional estimates (0.5 \* d1 \* d2 \* d3).

**Histologic analysis of orthotopic lung tumors.** Lungs were embedded in paraffin, step sections were done, and 5-μ-thick sections representative of 10 levels of the block were stained with H&E for routine histologic evaluation. Quantification of tumor area from histologic sections was done from digital micrographs using a Polaroid Sprintscan 120 and Adobe Photoshop (24). Data are reported as relative tumor size, defined as the integrated tumor area from 10 sections per lung in test animals compared with vehicle controls. Measurement of tumor areas was carried out in blinded fashion with respect to treatment groups.

**Survival study in orthotopic xenograft model.** NCI-H460 cells were injected orthotopically. After allowing 10 d for tumors to develop, mice were randomized into groups and treated with vehicle, apomab, chemotherapy, or combination as described above. Survival was followed for 15 wk (105 d).

**Statistical analysis.** Results are expressed as mean ± SE. To assess differences in tumor size between groups, one-way ANOVA was done; significant differences were subjected to post hoc analysis using Fisher’s PLSD method. Survival was compared by log-rank (Mantel-Cox) test. Median survival time was estimated from Kaplan-Meier analysis.

**Results**

**In vitro activity of apomab and chemotherapy on NCI-H460 cells.** As a prelude for the present studies, we examined the capacity of three NSCLC cell lines: H460 large cell carcinoma, H2122 adenocarcinoma, and SK-ME-S1 squamous cell carcinoma, to grow orthotopically in the lung parenchyma of mice. H460 cells gave rise to aggressively growing orthotopic tumors, consistent with earlier work (24). By contrast, H2122 cells or SK-ME-S1 cells, which readily form tumors after s.c. injection and respond well to apomab therapy (31), did not display a sufficiently high tumor-take rate orthotopically to permit reliable efficacy studies. We therefore focused our subsequent studies on H460-based models. Treatment of cultured NCI-H460 cells with apomab plus anti-Fc antibody resulted in a dose-dependent loss of cell viability (Fig. 1A). Combined...
treatment with Taxol, a chemotherapeutic agent that is frequently used in first-line therapy of NSCLC, markedly augmented the amount of apomab-induced cell death. Consistent with apoptosis induction, apomab plus anti-Fc antibody caused a dose-dependent stimulation of effector caspases, as measured by caspase 3/7 enzymatic activity (Fig. 1B), which was substantially enhanced by Taxol. Our previous studies show that Taxol alone has minimal effect on caspase processing of NCI-H460 cells (24). Immunoblot analysis of cell lysates indicated that Taxol induced little or no cleavage of caspase-8, caspase-9, and caspase-3, or the proapoptotic Bcl-2 family member Bid (as evidenced by the lack of significant depletion of the noncleaved proteins; Fig. 1C). In contrast, apomab stimulated detectable processing of caspase-8, Bid, and caspase-3, whereas the combination of both agents induced substantially greater cleavage of caspase-8, Bid, caspase-9, and caspase-3. These data suggest that the combination of apomab and Taxol results in greater caspase activation, leading to a more effective tumor cell kill than that induced by each agent alone.

Effect of apomab and chemotherapy on growth of s.c. tumor xenografts. To examine the activity of apomab in vivo, we first assessed its efficacy in a xenograft model in which NCI-H460 cells were injected s.c. into nude mice. When the mean tumor volume reached ~170 mm³, the mice were randomized into groups and treated with vehicle, apomab, Taxol plus carboplatin (chemotherapy), or the combination of apomab and both chemotherapy agents. Tumor volumes were monitored throughout the study (Fig. 2A). Tumors in vehicle-treated animals grew rapidly, whereas tumors in mice receiving apomab or chemotherapy alone grew more slowly and showed a partial delay in progression. In contrast, combined treatment with apomab and chemotherapy caused a slight tumor regression and further delay in tumor progression. Hence, whereas either apomab or chemotherapy alone similarly produced a partial attenuation in the aggressive s.c. growth of NCI-H460 tumors, the combination of both treatments caused some tumor shrinkage and a more effective delay in tumor progression.

TUNEL analysis of histologic sections from H460 tumors 24 hours after treatment indicated that apomab induced a substantial amount of apoptosis (Fig. 2B). By contrast, chemotherapy alone did not significantly induce apoptosis as compared with control, and combined treatment with apomab plus chemotherapy led to an apoptosis level comparable with that seen with apomab alone. Similar results were seen at 48 hours and 5 days after treatment, or by immunohistochemical staining with antibody to active caspase-3 (data not shown). Apomab binds to human and cynomolgus monkey DR5 but not to murine DR5. Nonetheless, we assessed the effect of the various treatments on normal cells by TUNEL analysis of histologic sections from nearby skin overlaying the tumors. We observed minimal amounts of TUNEL-positive cells in apomab and the combination treatment groups at 24 hours (Fig. 2C), as well as in mice treated with control antibody or chemotherapy (data not shown). Similar results were obtained at 48 hours and 5 days after treatment, or by active caspase-3 staining (data not shown).

Effect of apomab and chemotherapy on growth of orthotopic lung tumor xenografts. To investigate the activity of apomab against NCI-H460 tumors growing in an orthotopic tissue environment that may mimic the microenvironment in which primary lung tumors grow in cancer patients, we used a model in which the cells are surgically introduced into the pulmonary
interstitium. In this model, we initiated treatment 10 days after intrapulmonary injection of tumor cells. Before starting treatment, microCT imaging of the lungs was done to measure pulmonary tumor volume. Apomab was dosed over 15 days and chemotherapy was given over 5 days. On day 25 after study initiation, microCT lung imaging was again carried out for measurement of tumor volume, and the fold change in tumor volume in each animal was calculated. Finally, the lungs were removed for histology, and tumor area was determined by analysis of serial histologic sections.

Fig. 3. Effect of apomab and/or chemotherapy on growth of orthotopic lung tumor xenografts assessed by microCT. Ten days after intrapulmonary injection of NCI-H460 cells, nude mice received vehicle, apomab (10 mg/kg/d i.p. every 5 d for 15 d), chemotherapy (Taxol at 6.25 mg/kg/d s.c. for 5 d, plus carboplatin at 100 mg/kg, single i.p. dose), or the combination of both apomab and chemotherapy regimens. MicroCT imaging of the lungs was done before and after treatment. A, tumor volume measured by microCT before treatment. B, fold change in tumor volume measured by microCT as defined by posttreatment tumor volume - pretreatment tumor volume/pretreatment tumor volume in each animal. **, *P < 0.01 between the vehicle and each of the other three groups; #, *P < 0.05 between the combination and the chemotherapy or apomab group. Animal number was 15 to 16 per group. Chemo, chemotherapy.

Fig. 4. Effect of apomab and/or chemotherapy on growth of orthotopic lung tumor xenografts measured by histology (A) and correlation between tumor volume measured by CT and tumor area measured by histologic analysis (B). Ten days after intrapulmonary injection of NCI-H460 cells, nude mice received vehicle, apomab (10 mg/kg/d i.p. every 5 d for 15 d), chemotherapy (Taxol at 6.25 mg/kg/d s.c. for 5 d, plus carboplatin at 100 mg/kg, single i.p. dose), or the combination of both apomab and chemotherapy regimens. MicroCT imaging of the lungs was done before and after treatment. Lungs were removed for histologic studies after completing second microCT imaging. Relative tumor size, defined as the integrated tumor area of 10 histologic sections per lung in test animals compared with vehicle-treated controls (551.6 ± 118.7 mm²) was determined. *, *P < 0.05 between vehicle and chemotherapy or apomab group. ***, *P < 0.001 between the vehicle and combination groups. #, *P < 0.05 between the combination and chemotherapy or apomab group (n = 15-16 mice per group).
Tumor volume measured by microCT was not different in the four experimental groups before treatment (Fig. 3A). After a 15-day treatment regimen, tumor volume increased by 70.4-fold in the vehicle group, 6.7-fold in the apomab group, 7.1-fold in the chemotherapy group, and 0.4-fold in the combination group as compared with the respective pretreatment tumor volumes (Fig. 3B). Compared with the vehicle control, tumor growth was significantly inhibited by apomab ($P < 0.01$), chemotherapy ($P < 0.01$), or combination treatment ($P < 0.005$). The combination regimen produced greater inhibition in tumor growth compared with chemotherapy alone ($P < 0.05$) or apomab alone ($P = 0.07$). Thus, both apomab and chemotherapy exhibited significant antitumor activity, whereas the combination of both approaches exerted greater tumor inhibition, which was significant not only relative to vehicle control but also in relation to chemotherapy alone.

Quantitative analysis on histologic sections revealed that treatment with apomab, chemotherapy, or the combination reduced the mean tumor size respectively by 50% ($P = 0.0352; n = 15$), 49% ($P = 0.0386; n = 15$), or 94% ($P = 0.0002; n = 15$), respectively, as compared with vehicle control ($n = 16$; Fig. 4A). The reduction in tumor size was significantly greater in the combination group than in the chemotherapy group ($P = 0.0309$) or apomab ($P = 0.0277$) group. There was a high correlation between tumor volume measured by microCT and tumor area measured by histologic analysis ($r = 0.912; P < 0.0001; n = 57$; Fig. 4B).

Representative microCT images of one animal from each group and histologic sections of two animals from each group are shown in Fig. 5A and B, respectively.

**Effect of apomab and chemotherapy on survival of mice with orthotopic lung tumor xenografts.** To assess whether the observed antitumor activity translated into a survival benefit, we conducted a separate study in the orthotopic model. NCI-H460 tumors were allowed to grow for 10 days after intrapulmonary injection. The mice were then treated with apomab over 15 days, or chemotherapy over 5 days, or the combination of both, and survival was followed for 15 weeks (105 days). Animals were sacrificed if/when they displayed serious respiratory difficulty associated with lung tumor burden. Day 105 survival was 2 of 14 (14.3%), 4 of 14 (28.6%), 4 of 14 (28.6%), and 9 of 14 (64.3%), in the vehicle, chemotherapy, apomab, and combination treatment groups, respectively (Fig. 6). The survival benefit from treatment with chemotherapy ($P = 0.2634$) or apomab ($P = 0.2091$) alone did not reach statistical significance as assessed by log-rank (Mantel-Cox) analysis of the plots, whereas the survival benefit from the combined treatment was significant versus control ($P = 0.0023$) and versus apomab alone ($P = 0.0445$) or chemotherapy alone ($P = 0.0415$). The median survival time (MST) estimated from Kaplan-Meier analysis was 42.5 days in the vehicle group and prolonged by 41.2% in the apomab group (MST 60 days), 41.2% in the chemotherapy group (MST 60 days), and at least 147.1% in the combination group (MST >105 days), as compared with vehicle control. Indeed, MST was not reached in the combination group, as 9 mice (more than one half of the animals) still survived on day 105 suggesting a MST of more than 105 days in this group. Thus, the positive interaction of apomab with chemotherapy was reflected not only by the inhibition of tumor growth but also by a significantly improved survival.

**Discussion**

Apomab induces tumor cell apoptosis through DR5. It is a fully human monoclonal agonistic antibody that triggers...
It is believed that orthotopic tumor models may provide improved insight into the activity of a molecule in a clinical setting. However, an important technical hurdle has been that conventional means of monitoring s.c. xenograft tumors (e.g., external caliper measurements) cannot be used for assessing the growth of lung orthotopic tumors in living animals. Because there may be some variability of tumor growth after orthotopic injection of tumor cells, we used in vivo microCT imaging to assess tumor volume before and after treatment. MicroCT was used for the selection and grouping of tumor-bearing mice and for evaluating a change in tumor size after treatment in each animal. With this noninvasive imaging technique, animals can be compared with comparable tumor volumes to limit variation in each group. Because potential differences in tumor volume between treatment arms were largely eliminated, a further impediment to interpretation was avoided. The present study also shows a high correlation between tumor volume measured by microCT imaging and tumor size measured by histologic tumor assessment ($r = 0.912; P < 0.0001; n = 57$), indicating accuracy with the microCT method. MicroCT has been reported to detect lung tumor burden in a murine model of lung cancer induced by i.p. injection of the carcinogenic agent urethane (33). The present study clearly shows that in vivo microCT measures tumor volume precisely in a large number of mice with orthotopic lung cancer, as confirmed by quantitative histologic assessment.

We selected the NCI-H460 NSCLC cell line as a preclinical model, because our previous studies have shown that these cells form rapidly growing tumors in the lung after orthotopic injection in nude mice (24). MicroCT imaging showed that tumor volume by 25 days after H460 cell injection into the lung was increased by 70.4-fold compared with pretreatment tumor volume in vehicle-treated mice. This aggressive tumor growth was significantly inhibited by apomab or chemotherapy alone, whereas combination treatment exhibited a markedly greater inhibition than chemotherapy alone. Similarly, histologic analysis revealed that apomab or chemotherapy caused a significant reduction in tumor size relative to vehicle control, whereas the reduction in tumor size was substantially greater in mice treated with the combination compared with those treated with either monotherapy. Together, both microCT and histology showed that apomab exerted marked antitumor activity, which was further augmented on combination with clinically established chemotherapy in the orthotropic model of lung cancer. Survival is an important factor for preclinical and clinical studies on new anticancer compounds. Our results suggest the possibility that apomab or chemotherapy alone prolonged survival compared with vehicle control, but the differences did not reach statistical significance. However, the combination of both approaches significantly improved survival not only relative to vehicle control but also in relation to either monotherapy.

Apomab triggers apoptosis through the cell-extrinsic pathway, which involves direct recruitment and activation of caspase-8 through DR5 and the adaptor molecule Fas-associated death domain (31). In contrast, many chemotherapeutic agents initiate apoptosis by engaging the cell-intrinsic pathway, which involves activation of proapoptotic Bcl-2 family members, leading to the release of cytochrome C and Apaf-1, thereby activating caspase-9 (34). The initiator caspases (caspase-8 and caspase-9), in turn, activate downstream effectors such as caspase-3 and caspase-7, which execute the apoptotic demise of the cells. Our in vitro analysis suggests that chemotherapy sensitizes tumor cells to apoptosis induction by apomab through cross-talk between the intrinsic and extrinsic pathways that leads to enhanced caspase activation (3, 31). Whereas apomab-induced apoptosis was readily demonstrable in vivo by TUNEL or active caspase-3 antibody staining of tumor sections, chemotherapy induced minimal apoptosis by itself, and did not significantly change the level of TUNEL staining in tumor sections beyond the effect of apomab monotherapy. It is therefore possible that the positive antitumor interaction between the two types of therapy is based on the combined proapoptotic activity of apomab with nonapoptotic chemotherapy-induced effects (e.g., antiproliferative activity).

In conclusion, we examined the activity of the agonistic DR5 antibody apomab and its interaction with chemotherapy by assessing tumor growth and host survival in the NCI-H460 orthotopic lung cancer xenograft model. Both microCT imaging and quantitative histologic analysis showed that treatment with apomab, chemotherapy, or combination significantly inhibited...
tumor growth compared with vehicle, with the combination causing markedly greater reduction in tumor size relative to chemotherapy or apomab alone. Further, log-rank (Mantel-Cox) analysis revealed that the combination of apomab and chemotherapy significantly improved survival not only as compared with vehicle but also in comparison with apomab treatment or chemotherapy alone. A high correlation between tumor volume measured by microCT imaging and tumor size assessed by histologic analysis confirmed the accuracy of microCT for assessing tumor growth in this orthotopic lung cancer model. Thus, our findings indicate a positive interaction of apomab with chemotherapy as measured by inhibition of tumor growth as well as by improved survival. These preclinical results provide support for further clinical investigation of this type of antibody-chemotherapy combination in lung cancer patients.

Disclosure of Potential Conflicts of Interest

The authors are employed by and have an ownership interest in Genentech.

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