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CIMAvax EGF vaccine for stage IIIb/IV non-small cell lung carcinoma

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This case report documents the use of the CIMAvax Epidermal Growth Factor vaccine regimen in a 54 year old female with stage IIIb non-small cell lung carcinoma. Even after 48 mo since diagnosis her ECOG performance remains at zero. Further, this report documents a reaction to the vaccine of grade 3 severity not previously documented.

Introduction

Over 75% of patients with NSCLC present with stage III or IV disease.[1] At these stages concurrent chemoradiotherapy or palliative chemotherapy are the preferred treatments.[2] Used optimally, these conventional therapies offer a median survival time of approximately one year from the time of diagnosis.[3]

By comparison patients undergoing the experimental CIMAvax (Center for Genetic Engineering and Biotechnology) Epidermal Growth Factor (EGF) vaccine treatment regimen have demonstrated significant increase in survival time. It should be noted that the following quoted survival times in the CIMAvax trials are measured from time of inclusion and not time from diagnosis. Pooled data from three phase I/II randomized trials (n = 83, all of whom had had at least one line of conventional treatment) showed that, on average, vaccinated patients had a mean survival time of almost double that of concurrent unvaccinated controls (9.13 vs. 4.85 mo, $p < 0.02$).[4] A larger scale Phase II randomized controlled trial (n = 80) produced similar results.[5] It added that vaccinated patients under the age of 60 had an especially improved median survival time over control subjects (11.57 vs. 5.33 mo, $p < 0.02$). Due to its remarkable results, the vaccine has received Sanitary Registration in Cuba for advanced NSCLC. Our case took part in a Phase III trial currently underway.

The CIMAvax vaccine regimen works by inducing the patient's own immune system to produce antibodies against self-made EGF ligand. EGF is a mitogenic factor which plays an important role in cell proliferation through various pathways including KRas and JAK/STAT.[6] In NSCLC its overexpression positively correlates to shortened survival time.[7] By stimulating the immune system against circulating autologous EGF these tumorigenic pathways are disrupted.

Survival time has been found to be positively tied to the degree of seroconversion.[4,5] Those whose antibody titers rise above 1:64 000 sera dilution are termed Super Good Antibody Responders (sGAR). By contrast those that seroconvert but do not reach 1:4000 sera dilution are termed Poor Antibody Responders (PAR).[8] Those whose antibody titers are between PAR and sGAR are named Good Antibody Responders (GAR). sGAR patients survive longer than GAR. GAR patients in turn survive longer than PAR.[8,9]

An emerging discovery which may improve patient survival centers around the so-called "loop B" component of the EGF ligand. This peptide facilitates EGF binding to its receptor in the tumorigenic pathway. One trial found that patients in whom immune action centered against this peptide had a better prognosis.[10,11]

The CIMAvax regimen is still evolving. Issues such as scheduling, dosages and length of treatment are continually undergoing re-evaluation. Our case received cyclophosphamide pretreatment before her vaccination schedule (**Table 1**). 80% of those given cyclophosphamide before the CIMAvax course will demonstrate some anti-EGF activity.[4] Effectiveness is further enhanced if the vaccine is injected over multiple sites as our case was.[9] Doing so may involve more lymph node regions.[12]

The vaccine itself (developed and produced in the Center of Molecular Immunology) contains human recombinant EGF and a carrier protein in an adjuvant. Both the EGF and carrier protein (P64K) are produced by the Center for Genetic Engineering and Biotechnology. Trials have shown that the addition of P64K and adjuvant—Montanide ISA 51 (Seppic)—increase seroconversion rates while being low in immunogenicity themselves.[4,13-15]

Documented side effects are mild. These include tremors, headache, constitutional symptoms and arthralgia.[8,15] The theoretical side effect of autoimmunity has not been recorded in vivo.[16]

The objective of this article is to introduce practitioners to the potential of this vaccine, and describe a side effect not previously documented.

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Case Presentation

Fifty-four year old Madam FNM presented in December 2007 with a 2 mo history of worsening hemoptysis. This was associated with loss of weight and appetite and bone pain. A CT chest scan showed a 'large, lobulated, heterogeneously enhancing mass' at the posterobasal segment of the left lower lobe of the lung measuring 9 by 5.8 by 7.2 cm. Another smaller spiculated lesion was noted in the left upper lobe. A biopsy confirmed an infiltrating, moderately differentiated squamous cell carcinoma. The CT scan was negative for chest wall muscle involvement. Her bone scan was negative. She was diagnosed with stage T4N1M0-IIIb NSCLC.

Madam FNM was treated with 3 cycles of paclitaxel (260 mg) and carboplatin (415 mg) over 3 mo. This reduced the tumor to 7 cm by 6 cm by 5 cm. Concurrent chemoradiotherapy, 2 cycles of cisplatin (50 mg) and 60 Gy of radiation over 30 fractions then followed.

Two months after her chemoradiotherapy had ceased, Madam FNM agreed to take part in the CIMAvax regimen (**Table 1**). A pre-regimen CT scan demonstrated the lower lobe lesion to be 3 by 3 cm (**Fig. 1**). The left upper lobe lesion was less than 1 cm diameter with a loculated pleural effusion secondary to radiation. After 3 mo the tumor had shrunk to 2 by 2.1 cm (**Fig. 2**). By 6 mo the tumor shrank 30% from its original volume to 1.5 by 2.3 cm before stabilizing. In the same period her pleural effusion diminished while local lymph nodes became smaller.

Madam FNM did not report any side effects during the course of the regimen until her 17th round of injections. Within minutes of her injections she experienced an "excruciating" pain localized to the lumbar and loin in a similar distribution to that of renal colic. This is classed as a vaccination-related Grade 3 reaction.[17] It subsided after 10 min after treatment with IV chlorphenamine 10 mg, IV hydrocortisone 200 mg and IV tramadol 50 mg. Because of this she decided to withdraw from the CIMAvax regime, and since not experienced any further episodes of pain. The patient was not rechallenged with CIMAvax. Allergy testing was not performed.

A CT chest scan was performed three months after cessation (month 18) of treatment. There were "no obvious changes" in the size of the tumor since her last scan 6 mo prior (**Fig. 3**). At last followup—28 mo after stopping the vaccine—Madam FNM was well and enjoying stable health. Her ECOG status had remained at 0. At this point she had survived for 48 mo since diagnosis.

Table 1. Madam FNM's CIMAvax regimen.

Time	Action
Day minus 3	290 mg cyclophosphamide
Day 0, 14, 28	200 ug CIMAvax injected over 4 sites (ie 50 ug per deltoid and gluteus)
Every 28 d until withdrawal from regimen	200 ug CIMAvax injected over 4 sites (ie 50 ug per deltoid and gluteus)

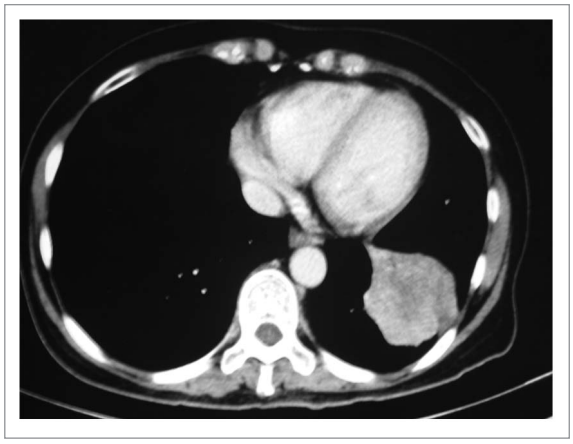

Figure 1. Pre-regimen CT chest, left lower lobe lesion 3 by 3 cm.

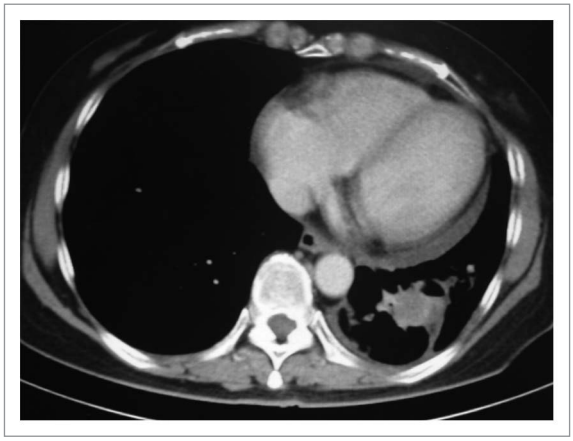

Figure 2. CT chest (month 3 from CIMAvax commencement), left lower lobe lesion 2 by 2.1 cm.

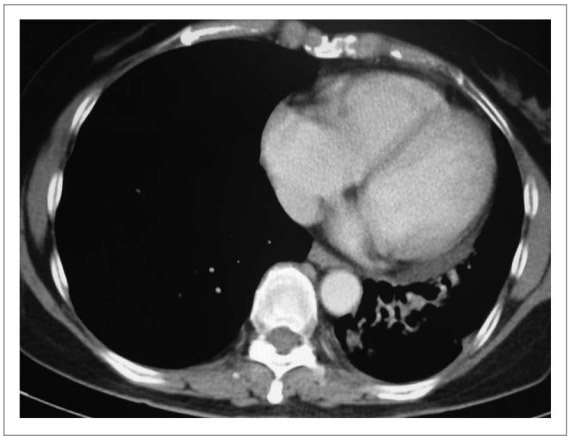

Figure 3. CT chest (month 18 from CIMAvax commencement), left lower lobe lesion 1.5 cm by 2.3 cm

Discussion

Madam FNM's survival—48 mo since diagnosis—has been remarkable. Ongoing vaccination is necessary to boost antibody titers back to peak levels.[4] Therefore it is interesting that her disease has not shown progression after her last injection some 28 mo previously. Her age may be a contributing factor—54 y old at time of vaccine commencement. A Phase II randomized controlled trial found that vaccinated patients under 60 y of age received increased survival times relative to unvaccinated patients. On the other hand those over 60 y old had no significant differences in survival.[5] Madam FNM's antibody titers were unobtainable. This is a limitation of this report. However it would be interesting to measure her anti EGF titers. Longer lasting and larger antibody titers have been successfully produced by EGF booster inoculations in animal models.[12] So far these attempts in humans have not elicited similar results.[15]

Madam FNM's side effect of back pain is unique to the authors. Successful treatment by antihistamine suggests that Madam FNM experienced an anaphylactoid reaction. These mediators can cause ureteric smooth muscle to spasm.[18] This may explain her renal colic-like symptoms. However the real mechanism is unclear. Trials involving vaccines including Montanide ISA 51, hu-EGF and P64K protein have been known to cause Grade 2 reactogenicity reactions.[19-21] These include some local inflammation and constitutional symptoms. While Montanide ISA 51 has been used extensively,[22] experience with hu-EGF and P64K is relatively new. Data from the Phase III study may shed more light on this reaction.

Conclusion

The CIMAvax vaccine regime offers hope in significantly extending survival time to those who have an otherwise short life expectancy. Further research is important in uncovering side effects. As well, further experimentation in methods of vaccine composition and delivery may well improve the CIMAvax regime's efficacy.

Author Contributions

J.Y.C. wrote the manuscript and R.K. was the physician overseeing Madam FNM's treatment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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