Faculty disclosure

There is no financial interests or relationships with any of the commercial supporters.
5-FU ointment for treating cholesteatoma

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5-FU (5-fluorouracil)

1. It is an anti-neoplastic agent, and its local application (ointment) is effective especially for skin tumors.

2. It is also effective for premalignant proliferative lesions of the skin such as actinic keratosis (Eaglstein et al, 1970).

3. Side effect is extremely rare in case of local application.
History of 5-FU treatment of cholesteatoma

the first report on the use of 5-FU on cholesteatoma

reconfirmed its clinical efficacy and safety

confirmed its efficacy in animal experiments

the first report from Japan

reported on experiences in 50 cases
5-FU ointment is applied on the surface.

A volume of half of a rice grain (2-3 mm³) is used with a cotton stick. Treatment is usually given for 3 - 4 times with an interval of 1 - 3 weeks. When necessary, ear drops containing antibiotics, steroids and/or anti-fungal agents are used.
First case I experienced
(Attic cholesteatoma, 20 y.o., man)

Before treatment

1 week after application of 5-FU ointment
First case I experienced
(Attic cholesteatoma, 20 y.o., man)

4 weeks after treatment

2 years after treatment
Case. Attic cholesteatoma (19 y.o., girl)

Eardrum

Before treatment

CT

After treatment

*
Case. Attic cholesteatoma (33 y.o., woman)

Before treatment

11 months after treatment

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Case. Attic cholesteatoma (70 y.o., man)

Before treatment

7 months after treatment
Case. Attic cholesteatoma (73 y.o., woman)

Before treatment

2 weeks later
Case. Attic cholesteatoma (54 y.o., man)

Eardrum

Before treatment

After treatment

CT

Before treatment

After treatment

*
Subjects
Aural cholesteatoma 103 patients (105 ears)  
(mean age: 53, children 2 ear)

Outer ear canal type  26 ears  
Attic type  54 ears  
Sinus type (Pars-tensa type)  19 ears  
Recurrent type  6 ears

Assessment
- Good - Condition without debris continued for at least more than a month
- Fair - Debris apparently decreased
- Poor - No change was seen
Results (105 ears)

- Good 53%
- Fair 24%
- Poor 23%

5-FU ointment was highly effective!

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Results of 5-FU treatment in various types of cholesteatomas

Ear canal type (26 ears)
- Good: 81%
- Fair: 15%
- Poor: 4%

Attic type (54 ears)
- Good: 41%
- Fair: 22%
- Poor: 37%

Sinus type (19 ears)
- Good: 37%
- Fair: 47%
- Poor: 16%

Recurrent type (6 ears)
- Good: 100%
This treatment is effective also on ear-canal cholesteatoma!

Probably because we can see the whole lesion and can easily clean up before treatment.
Case. EAC cholesteatoma (67 y.o., man)

Skin bridge was resected.

Two years later
Case. EAC cholesteatoma (69 y.o., man)

First visit
After 5-FU treatment

Two months after surgery.

One year after - completely cured.

5-FU treatment can be used in combination with surgery, especially for EAC cholesteatoma.
Side effects

- Hearing loss, tinnitus
- Erosion or ulcer formation
5-FU and ototoxicity?
Endocochlear potential (EP) after administration of 5-FU ointment (guinea pigs)

Hair cell findings one week after administration of 5-FU to middle ear

No abnormal finding on the hair cells in any turn

Light microscopic findings of the stria vascularis

Control side

Experimental side

N.S.

Mechanism of the favorable effect of 5-FU on cholesteatoma
Uncontrolled growth of cholesteatoma

Soft tissue underneath cholesteatoma epithelium containing chronic inflammation

Keratinocyte growth factor (KGF)

One of the growth factors of fibroblast, and is a cytokine primarily contributing to wound healing (Finch, et al, 1989, etc.).
KGF and its receptor (KGFR) in cholesteatoma tissue

KGF was seen in the stroma under the epithelium, and KGFR was seen in the basal layer of the cholesteatoma epithelium.

(Yamamoto-Fukuda T, et al., Lab Invest, 2003)
Experimental cholesteatoma with local application of KGF

**Methods**
Flag-hKGF vector was induced into the ear canal skin cells using electroporation in rats for 5 times.

Cholesteatoma developed in 12 out of 13 rats (92.3%)!

(Yamamoto-Fukuda T, et al., EUR Arch ORL, 2014)
Clinical study of 5-FU ointment on cholesteatoma tissue

Subjects:
77 cholesteatoma patients undergoing surgery (Age 10-85)
  1. 5-FU before surgery (12 ears)
  2. Without 5-FU treatment (65 ears)

Methods:
On the resected cholesteatoma specimens, KGF and KGFR were examined by immunohistochemical method.
Expression of **KGF** in cholesteatoma tissue

5-FU treated and untreated groups

Expression of KGFR in cholesteatoma tissue 5-FU treated and untreated groups

Take home messages
5-FU treatment for cholesteatoma

Good for:  
- Early-staged cholesteatoma  
- Inoperable cases (Underlying diseases, age, etc.)  
- Those who refuse surgery

Be careful:  
- Not to put it into the middle ear  
- Not to apply to patients with fistula  
- Periodical check by CT and audiogram

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Thank you for your kind attention.