Treatment of HIV Infection - Current Status and Future Directions

reported by Dr. M.H. Ho

Date:	10 December 1997
Venue:	Queen Elizabeth Hospital
Speaker:	Dr. David Ho
Organizer:	Department of Medicine, QEH.

The first half of the seminar was mainly about the virology of HIV virus. After infection with HIV, the virus replicates rapidly and then the level of viral load will decrease due to natural death of the virus. Finally, an equilibrium state is reached--virologic setpoint. This is the level at which the amount of virus replicated equals to those died. This virologic setpoint affects the long term outcome. The higher the setpoint, the worse the outcome. It is influenced by both viral and host factors.

There are two populations of infected cells. One is those which have rapid turnover. The productively infected CD4 cells is one example and it has a half-life (t1/2) of 1.1 day. The other population is in the dormant form. It includes long-lived cell population (monocytes, macrophages) which decays slowly, with a t1/2 of 14 days; latently infected CD4 cells with a t1/2 of 8.5 days. These two populations of cells act as a "reservoir" of virus even after treatment started.

Nowadays, the treatment armament only "eliminates" the virus from the circulation in the sense that the viral load is not detected by the current assay technique. A study measuring HIVmRNA showed the presence of virus in lymph nodes after HIV treatment. Multiple spliced (MS) HIVmRNA and unspliced (US) HIVmRNA were measured in serum, genital fluids, and lymph node tissue. MS HIVmRNA indicates ongoing replication of the virus and US HIVmRNA indicates HIVmRNA population. The result showed the presence of US HIVmRNA in lymph node tissue but absent in serum and genital fluid. It illustrated that there is still a population of HIV remaining dormant in the lymph nodes.

The lymphocyte turnover was increased in HIV infection in animal study (monkey). The CD4 proliferation and death rates were both raised in infected subjects.

The future research is aiming at overcoming the obstacle of these "dormantly" infected cells that harbour HIV. The strategy is to activate the latently infected CD4 cells by various cytokines (tumor necrosis factor, IL2) or anti-CD3 monoclonal antibody. These cells are then susceptible to the anti-viral agents.

Newer agents are now under research including integrase inhibitors and cold receptor inhibitors. The current anti-viral agents are only active against HIV-1 only. There is limited data on HIV-2 infection.

Questions were raised about failure of the "cocktail" treatment. Dr. Ho concluded that failure of the cocktail regime was due to three main reasons. Firstly, the patient was usually in the late stage of the disease. Secondly, drug non-compliance was another main cause. Lastly, the patient had been exposed to various kinds of monotherapy causing resistance of the virus. This made the choice of combination treatment difficult.

First Asia-Pacific Conference on Cutaneous Surgery and Laser Therapy

Update on Moh's Micrographic Surgery

reported by Dr. K.H. Lau

Date: 11 December 1997
Venue: Prince of Wales Hospital
Speaker: Dr. Richard Barlow
Organizer: CUHK (Co-sponsored by HKSDV)

CONVENTIONAL SURGERY VS. MOH'S MICROGRAPHIC SURGERY

Conventional pathological sectioning cuts specimen in a way similar to cutting a loaf of bread. In examining the margin in a specimen of skin malignancy, small extensions and strands of malignant cells can easily be missed by this traditional method of sectioning. As a result, Moh's micrographic surgery is derived for examining the whole resection margin of skin tumour excised and to minimize normal tissue destruction.

INDICATIONS OF MOH'S SURGERY

Moh's surgery with in situ tissue fixation is indicated in wide range of tumour excisions. It is commonly employed in the excision of morpheic or sclerotic basal cell carcinoma, especially in those with ill-defined border or multicentric in origin. Complicated tumours located in critical anatomical sites such as around eyelids or external auditory canal are best removed under Moh's technique. Re-excision of incompletely excised tumour is another indication. Tumour of larger than 2 cm in diameter is also best treated by Moh's surgery because of relative high chance of local or perineural spread and recurrence.

LIVE DEMONSTRATION

Dr. Barlow not only reviewed the surgical techniques with the audience, but also demonstrated the skill and important details that need extra caution during the real time live operation in the meeting. Curettage of the initial tumour mass, especially in a case of basal cell carcinoma, is preferred by Dr. Barlow. This procedure serves to debulk the main tumour mass and gives a much better delineation of the clinical border involved by tumour. In Moh's surgery, the surgical blade should cut at a 45 degree so as to obtain a sausage-shaped layer of skin which can be pressed down for sectioning. During the demonstration, Dr. Barlow illustrated the importance in mapping the excised specimen, divided into 4 quadrants with cut edges stained, to the anatomical structures in the patient. Four small skin incisions are nipped at the margin of the wound to delineate the 4 quadrants for reference. Frozen sectioning is performed to detect any tumoural involvement of the excised margin in the 4 quadrants. Hence, subsequent excision in any quadrant, if needed, can be located easily.

RECENT ADVANCES

Immunohistochemical Staining

Recognition of tumour cell in frozen section of excised tissue has its limitations. The thickness of the section may not be ideal, and tears and freezing artefact may affect interpretation. In order to overcome this problem, immunohistochemical staining technique has been used to augment the identification of tumour cells.

In principle, the tissue section is firstly incubated with an anti-tumour-cell-specific mucin monoclonal primary antibodies. Subsequent detection of the presence of these primary antibodies is amplified by the use of peroxidase conjugated anti-mouse secondary antibodies derived from rabbit. These secondary antibodies eventually give a strong colour signal. The whole process may take up to an hour.

Various primary antibodies have been developed for recognizing different tumour cells in the sections. AE1 (Biogenex) low molecular weight cytokeratin marker is used for recognizing tumour cells in squamous cell carcinoma. Marker antibody against cytokeratin (CK) 1 is used for basal cell carcinoma. Anti CEA (Dako) antibodies is used for extramammary Paget's Disease. Anti-CD34 (Becton Dickinson) antibody is used for labeling malignant cells in Dermatofibrosarcoma protuberans.

Immunohistochemical staining technique used in Moh's surgery has its own limitations. False negative results may occur due to technical error during specimen preparation which may lead to loss or alteration of marker antigen in the section. False positive nonspecific staining may also occur.

Paraffin Embedded Section

In order to increase sensitivity and specificity of tumour recognition, paraffin embedded Moh's section has recently been introduced. The advantage of paraffin embedded section is the relative ease in identifying tumour cells as compared with fresh frozen section or fixed section. The disadvantage of the technique is the need of more time for preparation (may take up to 1 day). Hence, the efficiency for obtaining the result ranks intermediate (as compared with the highly efficient frozen section and the least efficient fixed section).

Moh's Surgery with Paraffin Section in Melanoma

Moh's surgery has been used in the removal of melanoma in situ lesion. Conventional Moh's surgery has the difficulty in identifying the atypical melanocytes as there is no perinuclear retraction in these cells when prepared under frozen section. By the use of paraffin embedded section, identification of atypical melanocyte is much easier, hence making the use of Moh's technique possible in the treatment of melanoma in situ. Comparing with the conventional wide marginal excision, 0.5cm margin of normal skin (preferrably confirmed by the use of Wood's light) obtained by Moh's excision is believed to be adequate. In both cases, the depth of excision must be extended down to subcutaneous fat.

CONCLUSION

Moh's micrographic surgery has the advantages of low recurrence in tumour excision (<1% as compared with 8-10% quoted in conventional surgical or radiotherapy treatment for skin cancer). It also conserves normal skin which is very important for reconstruction of vital structures uninvolved by tumour growth.

Learning points:

Advances have been made to augment the identification of tumour cell in Moh's micrographic surgery by the use of immunohistochemical staining and paraffin sectioning.

However, two of the important drawbacks for Moh's surgery are firstly, the requirement of special surgical training, and secondly, this technique being time-consuming. Hence, this sophisticated treatment is only available in limited centres with the expertise.

Erbium-Yag Laser in Laser Resurfacing

reported by Dr. R.C.W. Su

Date: 12 December 1997
Venue: Prince of Wales Hospital
Speaker: Dr. Stanek, Dr. Scheflan
Organizer: CUHK (Co-sponsored by HKSDV)

Pulse CO_2 laser has been used for laser resurfacing, which is useful in treating wrinkles of the aging face and in treating acne scars. However laser resurfacing is limited in Asian skin because of prolonged erythema and post-inflammatory pigmentation.

The Erbium Yag laser emits wavelength of 2.94um which fits the unique absorption characteristics of tissue water. Erbium has ten times the absorption coefficient to water compared with CO_2, providing more efficacious ablation with less thermal tissue damage. There is faster healing time (re-epithelialize in 3-4 days), less postoperative erythema and pigmentation. This results in significantly less morbidity or side effect, and more satisfactory clinical result. The patient can get back to work much quicker.

When laser resurfacing the whole face or a large area, it is better to deliver laser light with the scanner mode (with a computerized pattern generator) to give a more even, homogenous or uniform effect. However for treating individual scars, manual or free hand mode would be more suitable for the localized effect.

The erbium laser penetrates only the most superficial part of the skin, reaching 20-30um per pass instead of 100um per pass with CO_2 laser. Hence four to five passes (5J/cm^2) with the erbium laser will be required to achieve the same depth as one pass of CO_2 laser. With CO_2 laser the depth of ablation decreases with each pass due to tissue desiccation, this means that the ablative effects of CO_2 laser is limited to one or two passes only. Erbium laser light does not cause tissue desiccation, but the endpoint of erbium laser is bleeding of dermal capillaries which occurs after several passes. The reason is because erbium laser does not have the coagulative and haemostatic effect of CO_2 laser. This limits the number of passes and depth achieved with erbium laser in resurfacing.

Erbium laser is most suited for fine lines and wrinkles. For deeper wrinkles and scars, the erbium laser may not achieve sufficient depth in resurfacing as the CO_2 laser in one session. Moreover the CO_2 laser is more versatile, with other surgical functions apart from laser resurfacing. Hence erbium laser supplements rather than replaces the CO_2 laser. New laser systems are being developed, namely the erbium-CO_2 laser, housing both CO_2 and erbium laser in one machine. It is possible to deliver erbium and CO_2 laser light separately or simultaneously in combination. The efficacy of such systems is currently being evaluated.

Learning points:

Erbium Yag laser will complement pulse CO_2 laser in laser resurfacing of scars and wrinkles in Asian skin. This laser is most suitable for younger professionals with fine wrinkles or scars, with faster healing time, enabling them to return to work quicker with less morbidity.