Liposomal chemo for KS

The use of HAART suppresses HIV production, which allows the immune system to begin repairs. As a result, previously hard-to-treat infections usually begin to respond to therapy and may go into remission.

In HIV positive people with a limited number of KS lesions (less than 10) and no other KS-related complications, research-dermatologists have recently recommended that doctors prescribe HAART. They suggest that the immune recovery associated with HAART will, in the medium- or long-term, cause these limited number of lesions to fade.

For people with more extensive KS or who have KS tumours that are affecting their internal organs, anti-cancer chemotherapy is required.

In the time before HAART, chemotherapy caused some lesions to regress and generally delayed the spread of new lesions and reduced the size of existing ones. However, chemotherapy rarely cured AIDS-related KS.

In the 1990s, new formulations of chemotherapy were developed. These formulations contained chemotherapy inside tiny balls of fat called liposomes. They caused less toxicity and resulted in better penetration of chemotherapy into tumours.

In addition to trapping drugs inside liposomes, pharmaceutical companies have added PEG (polyethylene glycol) to them. The process of adding PEG to another drug is called pegylation and results in a longer-lasting formulation of the drug. One drug that has been reformulated so that it is both in liposomes and pegylated is called Caelyx, or liposomal doxorubicin.

Short- vs. long-term

While the short-term response to products (whether they are drugs, vaccines or chemotherapy) is well publicized by pharmaceutical companies, patients, their doctors and payers (such as drug formularies and insurance companies) are interested in long-term impacts.

So researchers at several Spanish hospitals reviewed health information collected from their patients with AIDS-related KS between 1997 and 2006 to assess the long-term effectiveness of liposomal anti-cancer therapy. All patients had received pegylated liposomal doxorubicin (PLD; Caelyx) as part of two studies. Their findings suggest that the use of PLD is very effective in moderate-to-advanced KS—relapse rates were low. However, the death rate was relatively high and the reasons for this are explored later in this report.

Study details

Researchers analysed data from two clinical trials. In the first study, they assessed the safety and effectiveness of PLD against AIDS-related KS. In the second study, they assessed the effect of HAART and PLD on KS. For the purposes of the combined study, the researchers looked at the long-term outcomes—KS, survival and complications.

In total, there were 98 participants who were evaluated. Their average profile was as follows:

- 4 females, 94 males
- age – 40 years
- all participants had at least 10 KS lesions on their skin or lesions in the mouth and internal organs; nearly 30% had KS on or near major internal organs/systems such as the lungs and intestine
- CD4+ count – 150 cells
- viral load – 16,000 copies
• all participants were taking HAART
• 75% of participants tested positive for HHV-8

Participants received PLD intravenously at a dose of 20 mg per square metre of skin, once every three weeks. Each of these dosing periods is called a cycle. On average, participants received nine cycles of PLD. Some participants were monitored for up to eight years.

Results—Initially

Response to therapy varied, but a substantial proportion of participants (75%) achieved some degree of benefit as follows:

• 48 people (49%) recovered from KS
• 27 participants (28%) had a partial recovery—lesions shrank by at least 50% in size and/or there were 50% fewer lesions after therapy

But there were some participants who did not benefit from PLD, as follows:

• 13 (15%) patients had little or no improvement
• 7 participants died while receiving PLD
• 3 participants did not complete their PLD regimens, probably because they were not effective

Results—Relapse

Of the 75 participants who had a favourable response (either a complete recovery or only a partial regression of lesions) researchers were able to report the long-term results on 61. These 61 people were monitored for an average of four years after their chemotherapy was complete.

In total, eight participants had their KS lesions return. In five people, this happened within one year of stopping chemotherapy.

Participants who relapsed tended to have lower CD4+ counts when they initially began chemotherapy or had low CD4+ counts after they completed chemotherapy.

Concern over deaths

Death rates were relatively high in this study and the possible reasons for this are complex and discussed later. Here are the overall details concerning deaths:

About 30% (29 out of 98 participants) died over the course of the study, as follows:

• 8 patients died while being treated for KS
• 9 patients died within one year after stopping chemotherapy
• 12 patients died more than a year after the end of their chemotherapy

The researchers noted that only three participants died from complications related to worsening KS. However, eight people died from serious blood and viral infections.

What caused additional concern was that in the remaining 19 patients all but two died from tumour-related complications. However, none of the tumours were KS—they were different forms of lymphoma. Participants died from lymphoma-related complications at the rate of about 2% per year. Death rates in KS studies now that HAART is available are generally much lower.

All patients with lymphoma tested positive for HHV-8. The significance of this finding will be discussed later.

Explanations

In reviewing the Spanish study, other researchers have noted the unexpected and high death rate. One explanation may be that patients in the Caelyx study were quite ill, given their extent of KS. However, this does not account for the many new cases of lymphoma that occurred after treatment with Caelyx.
A diagnosis of KS can be followed by subsequent diagnoses of cancer several years later. Both KS and lymphoma are associated with HHV-8 infection. Given that the immune suppression from HIV infection persists, even in HAART users, it is possible that this particular group of patients was more susceptible to cancer-causing viruses. However, high rates of death and subsequent lymphoma have not been noticed in other KS studies.

Another possibility is that prolonged exposure to chemotherapy, in this case doxorubicin, may have increased the risk of lymphoma. A previous study in HIV negative people with cancer suggests the possibility that exposure to doxorubicin may have played a role in the subsequent development of a second cancer such as leukemia or lymphoma.

So what to do? Experts in AIDS-related KS writing an editorial in the journal *Clinical Infectious Diseases* have suggested that HAART be the treatment of choice for mild or limited KS (fewer than 10 lesions and no lesions in the mouth or throat and no KS-related water retention). Close monitoring should be done to ensure that no new lesions appear and that over the medium- and long-term, KS lesions regress. If a few new skin lesions do appear, doctors should consider local treatment for them, remembering that HAART can help the immune system fight KS but that this immune response “may be delayed by several months or years,” according to the editorial.

In more serious cases, where KS is affecting an organ or is life-threatening, the experts recommend the following course of action:

“HAART should be associated with adjuvant therapy, such as taxanes (Taxol) or liposomal anthracyclins chemotherapies. Evaluation of the response to therapy should be performed regularly to prevent both early and late complications of chemotherapy and to avoid excessive dosages of chemotherapy in this population, which is at risk of developing lymphoproliferative disorders.”

REFERENCES:

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