Cutaneous T-Cell Lymphoma Case Study

LIGAND®
PHARMACEUTICALS

CASE

A 53-year-old woman has recently moved into your area and seeks your opinion regarding further treatment options for cutaneous T-cell lymphoma. Two years ago she was diagnosed with Sézary syndrome (SS). She was initially treated with extracorporeal photopheresis. She had a very good partial response but her disease relapsed.

She was subsequently treated with interferon. She has had an excellent response for the last eighteen months, but is now experiencing increased redness and scaling of her skin and cracking of her skin, particularly of her palms and soles. She complains of constant chills and shedding of her skin, and due to this, she has been confined to home. She has been unable to tolerate any increase in her interferon dose.

LABORATORY FINDINGS

Lab: WBC=15,000 with 50% lymphocytes

- CBC is otherwise normal
- Serum chemistries are normal, with the exception of creatinine 1.5
- Cholesterol is normal
- Fasting triglycerides 535
- Thyroid function is normal
- Chest film and CT of the abdomen and pelvis are unremarkable, as is her bone marrow exam. Flow cytometry of her peripheral blood shows her lymphocytes to be 90% CD4 positive, 3% CD7 positive.
- On physical exam she was found to have a 1 centimeter left groin lymph node.

TREATMENT DECISION

How would you now treat this patient since she is clearly failing her current therapy?

1. CHOP
2. Total body electron beam radiotherapy
3. Pentostatin
4. Diphtheria-IL2 fusion toxin (ONTAK®)
5. Methotrexate
6. Other

RESPONSES FROM OTHER COMMUNITY AND ACADEMIC HEMATOLOGISTS / ONCOLOGISTS[1]

CHOP	8%
Total body electron beam radiotherapy	15%
Pentostatin	0%
Diphtheria-IL2 fusion toxin (ONTAK®)	77%
Methotrexate	0%
Other	0%

DISCUSSION

Mycosis fungoides (MF) is an indolent primary cutaneous T-cell lymphoma (CTCL) that may progress from localized skin lesions to systemic disease. Sézary syndrome is a distinct variant characterized by generalized erythroderma and circulating cerebriform cells in the peripheral blood. The malignant cell in both diseases is a mature T-cell, usually with a CD4-positive, CD8-negative phenotype. Among the treatment modalities used in these diseases are skin-directed therapy, and single-agent and combination systemic chemotherapy. This patient has an advanced presentation with blood and lymph node involvement and has been previously treated with systemic therapies. Your treatment decision should consider her prior treatment; goal of therapy, such as preserving immune function; and future treatment options since this is a chronic disease that is likely to relapse, despite your treatment choice.

Diphtheria-IL2 fusion toxin (denileukin diftitox, ONTAK®)
Denileukin diftitox (DAB_{389}IL-2, ONTAK®) is approved by the FDA for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor. Denileukin diftitox is capable of inhibiting protein synthesis in cells that express the IL-2 receptor (IL-2R), resulting in cell death.[2]

A phase III study of denileukin diftitox was completed in patients with CTCL, whose tumors expressed the IL-2R as determined by immunohistochemical staining. In this study, the 73 treated patients were stratified by stage (I-IIA and IIB-IV) and randomized to receive denileukin diftitox at a dose of either 9 mcg/kg/day or 18 mcg/kg/day x 5 days repeated every 21 days for up to 8 cycles, as tolerated. All patients had malignant cells expressing CD25 (CD25+), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; the median number of prior treatments was 5. The overall response rate was 30%, with CR occurring at both dose levels. A slightly higher response rate was seen in patients who received the higher dose.[3]

For this patient, denileukin diftitox was chosen particularly for its lack of myelosuppression and high rate of response in heavily pre-treated patients. Denileukin diftitox is generally well tolerated and provides a rapid onset of response. Onset of response is generally seen after the second cycle (6 weeks) with best responses seen around the fourth cycle of therapy. Symptomatic relief is seen in about 60% of patients.[3]
Seventy-seven percent of community and academic hematologists and oncologists participating in a recent review of this case study selected denileukin diftitox (DAB_{389}IL-2, ONTAK®) as the treatment they would most likely administer to this patient.[1]

CHOP/Combination Chemotherapy: In MF, most chemotherapy regimens result in temporary palliative control with a median duration of response less than 1 year. The major toxicities of these drugs are neurotoxicity and prolonged immunosuppression, leading to opportunistic infections. Patients with advanced disease often have impaired immune function due to the loss of cytotoxic T-cells and often develop opportunistic infections such as herpes simplex, other viral infections, as well as bacterial and fungal infections. MF and SS are chronic diseases. Anthracycline-based regimens have a cumulative dose limit, therefore other chemotherapies such as gemcitabine could be considered before anthracycline based combination chemotherapies.

Total Skin Electron (TSE) beam radiation has proven efficacy in treating MF. Total skin radiation is an efficient monotherapy for patients with erythrodermic mycosis fungoides (T1-T3). Radiation may be most efficacious in Stage III, with no blood involvement. There is limited published evidence regarding the efficacy of total skin electron beam radiation for patients with the diffuse erythrodermic (T4) form of mycosis fungoides[4]. When there is blood, lymph node, or visceral involvement, combined modality therapies should be explored. Additionally, TSE beam is a complex technique that requires a dedicated radiation team, involving physicists, radiotherapists, and radiation oncologists. A center must treat a sufficiently high volume of patients to justify the development of a TSE center. This patient, however, has Sézary syndrome (SS) as evidenced by the high percentage of circulating T-cell lymphocytes. In summary, for this patient with blood and lymph node involvement, TSE beam radiation would likely have a very short duration of response and other modalities should be explored.

Antineoplastic Antibiotics like pentostatin would also be an option in advanced disease. Mercieca et al. showed an overall response rate of 32% using pentostatin at 4 mg/m^2/wk for the first 4 weeks and then every 2 weeks until maximal response, with the best responses seen in SS patients.[5] When used at lower doses, immunosuppression and myelosuppression may be lessened.

Other: Oral bexarotene (Targretin®) has been approved by the FDA for use in all stages of refractory mycosis fungoides and has a response rate of 45% in patients with CTCL. Hypertriglyceridemia, the most common adverse event, occurs in 80% of treated patients. This patient has triglycerides of 535 at baseline. Targretin at a dose of 300mg/m^2/day is likely to increase her triglycerides. If there were time to control her triglycerides with a statin, then Targretin would be an option. This patient, however, is in need of treatment immediately since her symptoms are significant enough to keep her home bound.[6]

REFERENCES

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