Secondary Malignant Neoplasms in 71 Patients With Sézary Syndrome

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Background: Sézary syndrome (SS) is characterized by a malignant proliferation of CD4+ve T cells, which may result in a degree of immunoparesis. Immunosuppression is associated with an increased incidence of internal malignant neoplasms and a high rate of nonmelanoma skin cancer, particularly squamous cell carcinoma. Therefore, we reviewed the incidence of secondary malignant neoplasms in patients with SS.

Observations: Of 71 patients with SS, 16 (23%) developed 19 secondary and tertiary malignant neoplasms. These malignant neoplasms included 8 cutaneous squamous cell carcinomas, 2 squamous cell carcinomas of the oral mucosa, and 9 other internal malignant neoplasms. The incidence of internal malignant neoplasms was twice that reported in patients of similar age treated for Hodgkin disease (P = .02). Furthermore, the incidence of cutaneous squamous cell carcinoma in the cohort was 42 times that observed in a study conducted in England of an age-matched population (1657 per 1 × 10^5 vs 39 per 1 × 10^5 person-years [95% confidence interval, 626-2856]).

Conclusions: A number of therapeutic modalities for SS are known to be carcinogenic. We compared the different therapeutic modalities received by our patients and found no significant difference between the total cohort of patients with SS and the patients who developed secondary malignant neoplasms. These data indicate that the high incidence of secondary malignant neoplasms in patients with SS is due, at least in part, to the disease itself. The clonal proliferation of CD4+ve T cells and the relative lymphopenia (compared with a healthy population) of nonneoplastic T cells may result in compromised immunosurveillance, so that early neoplasia, whether arising spontaneously or as a result of therapy, are not dealt with appropriately.

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SEZARY SYNDROME (SS) is the leukemic form of primary cutaneous T-cell lymphoma (CTCL). It is an aggressive disease and patients with SS have a median survival of less than 3 years. It is characterized by a malignant proliferation of CD4+ve helper cells. In patients with SS, the CD4 count may be markedly elevated, but, compared with healthy individuals, there is a relative lymphopenia of normal T cells leading to a degree of immunoparesis that may be severe. Immunosuppression is known to be associated with an increased rate of malignant neoplasms, for example, in renal transplant recipients receiving immunosuppressive therapy.

Many of the therapeutic modalities used to treat SS are known to be carcinogenic. Treatment with psoralen–UV-A (PUVA) increases the risk of nonmelanoma skin cancer, and chemotherapy is known to increase the risk of subsequent malignant neoplasms. In addition, there is a report of 2 patients with CTCL who developed cutaneous squamous cell carcinomas (SCCs) while receiving treatment with extracorporeal photopheresis (ECP).

We reviewed the incidence of secondary malignant neoplasms in our patients with SS. We compared the incidence of SCC in the cohort with the incidence in a study of an aged-matched population in England, patients with psoriasis treated with high-dose PUVA, and a study conducted in England of renal transplant recipients. We also compared the number of internal malignant neoplasms with those occurring in patients who were treated for Hodgkin lymphoma.

To determine whether the development of secondary malignant neoplasms in patients with SS is related to specific therapeutic modalities, we compared the type and number of treatments received by all the patients in the cohort with that of patients with secondary malignant neoplasms, those with tertiary malignant neoplasms, and those with cutaneous SCCs.
The cohort included 71 patients, aged between 41 and 84 years at time of onset of SS, who underwent a mean follow-up of 6.8 years. A total of 19 malignant neoplasms occurred in 16 (23%) of the 71 patients. Of the total cohort, 8 patients (11%) developed cutaneous SCCs and 11 patients (15%) developed internal malignant neoplasms, 2 of which were SCCs of the oral mucosa. Three patients (4%) developed tertiary malignant neoplasms. Table 1 lists the ages at onset of SS, the ages at onset and sites of secondary and tertiary malignant neoplasms, and outcome of the 16 patients. The mean age at onset of SS in the patients who developed secondary malignant neoplasms was younger than that of the Sézary group as a whole (62 vs 68 years, respectively). The mean age at onset of the development of the secondary malignant neoplasm was 69 years, and the mean time from onset of SS to the diagnosis of the secondary malignant neoplasm was 7 years.

Of our patients, 15% developed internal malignant neoplasms. This percentage is significantly higher than 5% (P<.001; CI, 8%–26%) of all patients and 7% of the patients aged 55 to 85 years (P = .02) in a study6 of 10 472 patients treated for Hodgkin lymphoma who developed secondary malignant neoplasms during a mean follow-up of 7.1 years.

Of the 16 patients, 3 developed tertiary malignant neoplasms (Table 1): 1 had an endometrial adenocarcinoma and developed a cutaneous SCC of the lower leg, 1 had systemic Hodgkin lymphoma and developed a cutaneous SCC of the nasolabial region the following year, and 1 had a cutaneous SCC of the ear and subsequently developed pancreatic adenocarcinoma. Only 1 patient developed a second lymphoma (Hodgkin lymphoma).

Of the 71 patients with SS, 56 (79%) were treated with chemotherapy, 19 (27%) with intravenous multiagent chemotherapy, 55 (77%) with single-agent oral chemotherapy including chlorambucil (no one had developed a second hematologic malignant neoplasm), and 7 (10%) with single-agent intravenous chemotherapy (Table 2). In addition, of the 71 patients, 49 (69%) were treated with ECP, 40 (56%) with PUVA, 15 (21%) with superficial radiotherapy, and 8 (11%) with total skin electron beam radiation. Most of the patients in the cohort received more than 1 type of therapeutic modality: 28 (39%) received PUVA and ECP and 34 (48%) received PUVA and chemotherapy. Of the 16 patients with secondary malignant neoplasms, 12 (75%) were treated with chemotherapy, 10 (63%) with PUVA, 10 (63%) with ECP, 1 (6%) with total skin electron beam radiation, and 1 (6%) with superficial radiotherapy.

The type and number of treatments did not differ significantly between the patients who developed secondary malignant neoplasms and the whole cohort. There was no significant difference between type of chemotherapy treatment received by patients who developed secondary malignant neoplasms, tertiary malignant neoplasms, and cutaneous SCCs compared with the whole cohort. The mean number of therapeutic modalities received by patients who developed secondary malignant neoplasms was 2.13 and, by those who did not, 2.68.

Cutaneous SCC developed in 8 (11%) of the 71 patients at a mean age of 67 years. This is an incidence of 1657 per 1 × 10^9 person-years (P = .001; CI, 626-2856), which is significantly higher than the incidence of 39 per 1 × 10^9 person-years (P<.001) in patients aged 65 to 70 years and 369 per 1 × 10^9 person-years (P = .001)
in patients aged 85 years and older from a study conducted in England.

Of the 8 patients who developed cutaneous SCCs, 6 (75%) were treated with chemotherapy, 4 (50%) with ECP, 4 with PUVA, and no one with any other form of radiotherapy. The median cumulative PUVA dose of the other 4 patients was 70.5 J/cm² in 52 treatments, similar to the median PUVA dose of 67.5 J/cm² in 40 treatments received by patients in the total cohort who did not develop cutaneous SCCs. A study of 551 patients with psoriasis treated with PUVA observed 9 cutaneous SCCs during a 10-year follow-up, which is an incidence of 350 per 10⁵ person-years. This incidence is significantly lower than the incidence of cutaneous SCC in our cohort, which was 1657 per 10⁵ person-years (P = .001; CI, 626-2856).

A study of 918 renal transplant recipients, 3% developed cutaneous SCCs. The number rose to 6% 10 years after transplantation. This incidence (550 per 10⁵ per-person-years) is significantly lower than the incidence (1657 per 10⁵ person-years) of SCC in our cohort (P = .006; CI, 626-2856).

COMMENT

Our study revealed a high percentage (23%) of secondary malignant neoplasms in patients with SS. Eleven patients (15%) developed internal malignant neoplasms; this percentage is significantly higher than 5% of all patients and 7% in the age-matched patients treated for Hodgkin lymphoma who developed secondary malignant neoplasms (P < .001).

Sézary syndrome is a disseminated form of CTCL, and the incidence of secondary malignant neoplasms may be...
more accurately compared with the incidence in patients with advanced Hodgkin disease. In a study conducted in England of 164 patients with advanced Hodgkin disease (stages IIB, IVA, or IVB), 10 patients (6%) developed internal malignant neoplasms during a median follow-up of 14 years; this percentage is significantly lower than that in our cohort (P = .01; CI, 8%-26%).

Previous studies9,10 have suggested that the risk of secondary malignant neoplasms increased in patients with CTCL. In a study of 544 patients with CTCL, 35 (6%) developed secondary neoplasms during a mean follow-up of 3.1 years. Of 26 patients with SS, 3 (12%) developed secondary malignant neoplasms. Another study10 of 71 patients with mycosis fungoides reported cutaneous SCC in 3 patients (4%), and another 3 patients (4%) developed internal malignant neoplasms during a mean follow-up of 8.3 years. This study concluded that the risk of secondary malignant neoplasms in patients with mycosis fungoides was relatively small and likely to be related to the therapy. However, unlike SS, which is an aggressive form of CTCL, mycosis fungoides is a low-grade form of CTCL in which blood involvement is not usually present. Our cohort and the mycosis fungoides study group are of equivalent size and age. In our cohort, we found an incidence of cutaneous SCC (11%) more than twice that seen in patients with mycosis fungoides (4%). In addition, the incidence of internal malignant neoplasms was 4 times greater (15%) in our cohort than it was in patients with mycosis fungoides (4%).

The incidence of cutaneous SCC in our cohort, with a mean age of 67 years, was 1657 per 105 person-years, which is significantly higher than the incidence of 39 per 105 person-years in the patients aged 65 to 70 years and 369 per 105 person-years in patients aged 85 years and older in a study conducted in England. This equals a 42 times greater risk of cutaneous SCC in our cohort compared with the age-matched population in England. The incidence of cutaneous SCC observed in our cohort may have resulted from the treatments, particularly PUVA and chemotherapy, which are known to increase the risk of nonmelanoma skin cancer.11,12 However, we compared the use of PUVA, systemic chemotherapy, ECP, superficial radiotherapy, and total skin electron beam radiation and found no significant difference in the types and numbers of treatments received by the whole cohort and patients with secondary malignant neoplasms, those with tertiary malignant neoplasms, and those with cutaneous SCCs.

It has been shown that PUVA therapy increases the risk of nonmelanoma skin cancer and that this risk increases with the number of PUVA treatments.13 Preliminary data from one study suggested that there might be a higher carcinogenic risk in patients with CTCL who were treated with PUVA than in patients with psoriasis treated with PUVA. In our cohort, 4 of the 8 patients who developed cutaneous SCC had never received PUVA or any other form of radiotherapy. The median cumulative PUVA dose was 70.5 J/cm2 in the other 4 patients and was similar to the median cumulative dose of 67.5 J/cm2 in the whole cohort. The incidence of cutaneous SCC is significantly higher in our cohort than that reported in a study of 551 patients with psoriasis treated with PUVA, although the mean cumulative PUVA dose in the patients with psoriasis was much greater (3015 J/cm2). Another study12 of 246 patients who received PUVA, a median cumulative dose of 654 J/cm2, reported a risk of nonmelanoma skin cancer 1.4 times greater than in the United Kingdom population. By contrast, we found a 42 times increased risk of cutaneous SCC in our patients with SS. Since 4 patients who developed cutaneous SCC had never received PUVA or any form of radiotherapy, it seems likely that there is an inherent susceptibility to the development of SCC in patients with SS.

There was no significant difference in the number of patients receiving chemotherapy in the whole cohort (56 [79%] of 71) compared with those who developed an additional malignant neoplasm (12 [75%] of 16). Of the patients who were treated with chemotherapy and developed a secondary malignant neoplasm, most (10 [83%) of 12) received single-agent oral chemotherapy. Immunosuppressant therapy is known to increase the risk of secondary malignant neoplasms and, in particular, cutaneous SCCs. However, the incidence of SCCs in our study was greater than that in the study of renal transplant recipients 10 years after transplantation.

Treatment with alkylating agents, such as chlorambucil, increases the risk of developing secondary leukemia.13 Of the 71 patients, 55 (77%) received chlorambucil; however, no one developed a secondary hematologic malignant neoplasm. One patient developed Hodgkin lymphoma, but this patient had not received any prior chemotherapy. Nineteen patients (27%) received intravenous multiagent chemotherapy; 2 (10%) of these patients subsequently developed secondary malignant neoplasms. This percentage is lower than that of the whole cohort (16 [23%] of 71). Of the 8 patients who developed cutaneous SCCs, 50% received ECP, a lower percentage than that of the whole cohort (49 [69%] of 71). This finding does not support the theory by Nehal et al14 that ECP may compound the risk of cutaneous SCC in patients with CTCL.

The incidence of malignant neoplasms in patients with SS tends to increase with age; however, the patients who developed secondary malignant neoplasms were diagnosed as having SS at a younger age than those in the whole group (62 vs 68 years). The mean time from onset of SS to diagnosis of a secondary malignant neoplasm was 7 years.

We have not found a significant difference between the types and numbers of treatment modalities received by the whole cohort, patients with secondary malignant neoplasms, those with tertiary malignant neoplasms, and those with cutaneous SCCs. Based on our data, we think that the high incidence of secondary malignant neoplasms in patients with SS is due, at least in part, to the disease itself. Thus, the clonal proliferation of CD4+ve T cells and the relative lymphopenia of normal T cells may result in a degree of immunosuppression such that early neoplasia, whether arising spontaneously or as a result of treatment, is not dealt with appropriately.
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REFERENCES


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