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Gemcitabine Based Chemotherpy and Maintenance with Thalidomide in Untreated Patients with Mycosis Fungoide

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ABSTRACT

Mycosis fungoides is the most common of cutaneous T-cell lymphomas, until now the best treatment has not been defined, probably because actual treatments are palliative, and when the tumor is refractory/relapse , response and outcomes are poor 'Thus we developed an regimen with gemcitabine- based combined chemotherapy, two drugs with proven efficacy in T-cell lymphomas , and dexamethasone, if the patient achieved complete response , they were allocated in an proportion 1:1, to received thalidomide in 21 of 28 days cycles by 3 years One hundred and twenty-six patients recruit ,122 (88%) achieved complete and were allocate to received thalidomide or control group. Actuarial curves at 10-years, show that improved outcome: progression-free survival was better in patients who received maintenance: 85% (95% Confidence interval (CI): 78%-93%) compared with control group: 54 % (95% CI: 48% - 59%) (p, 0.001), and overall survival were 87% (95%CI: 82% -94%) and 53% (95%CI: 47%-61%) (p, 0.001) respectively. Toxicities were minimal and well controlled.

We conclude that initial treatment in mycosis fungoides will be more aggressive, to improve outcome.

Keywords: Mycosis Fungoides; T-Cell Lymphomas; Thalidomide; Chemotherapy

Introduction

Cutaneous T-cell lymphomas are considered a group of extranodal non-Hodgkin lymphomas origin of T-cell lymphomas. The most common presentation is mycosis fungoides (MF) that account for 60 % to 77% ; although is considered a rare presentation , has been observed that an increase the number of patients in the

last years. Until now, the best treatment has not been defined, multiples studies has been performed, but neither offer conclusive evident , it is appear that some studies have been employed with an end-point conservative , only to disappear the cutaneous lesions, but ,no to treat to achieve a complete response (CR), waiting to relapse, to begin another palliative treatment. Taking in consideration that MF have an slow growth, the use of a regimen minimal toxicity could be better schedule; until the disease show an aggressive conduct, and more aggressive treatment are necessary. However, an this time biological, as interferon, retinoids or a single drug are employed. Aggressive chemotherapy is employed with an aggressive form of MF with, advances stages, and multiple tumor lesions.

Thus, CR is achieved in a minor of patients: 12 % to 26 %, with an progression-free survivaql (PFS), of 6 to 9 months, and overall survival minor of 12 months [1-10]. Thus, we developed an program with gemcitabine-based regimen, and two agents that have show efficacy in T-cell tumors, an steroid [8]. If CR is achieved, the presence of relapse suggested that tumor cells remain alive and are the cause of relapse, immunodulators agents has been employed, but lenalidomide have more toxicities, delay or diminished doses are necessary to continue an treatment, and in some instances has been associated with development of a second neoplasms: 18 to 30 %, thus we employe thalidomide at low-doses [9].

Patients and Methods

Patients with confirmed pathology and immunochemistry of MF (CD27 +, CD3+, CD77+) previously untreated, age > 18 years with no upper limit, stage IIB and IIIB, performed status < 2, without severe comorbidities, were including in the study. The trail was approved by the Ethical and Scientific Committee of our Institute, all patients signed and inform consent to participate in the study.

Chemotherapy

Gemcitabine 1000 mg/m^2 days 1 and 8 of each cycle, for 6 cycles. Methotrexate 400 mg/m^2, day 2 and 9 , followed by folinic acid 24 hours after. Etoposide 400 mg/m^2, days 2 and 3. Granulocyte factor stimulant granulocyte, was administered days 2 to 7, and 9 to 12, to diminished the risk of severe granulocytopenia. Radiotherapy, involved field, 30 Gy, was administered at sites with tumor > 5 cm, if after radiotherapy show suspicious lesions; biopsies were performed. At the end of treatment, if the patient achieve CR, were allocated in an proportion 1:1, to received maintenance thalidomide, 100 mg, oral, days 1 to 21, of 28 days of every cycle. The maintenance therapy was administered by 3 years.

Results

From June 2007 to December 2018, 132 patients were identified to participate to the study; 6 patients refused to participate; thus 126 patients were enrolled, demographic characteristics are show in Table 1, no statistical difference in gender, age, stage, were observed. Lactic dehydrogenase were elevated in 13 cases, and beta 2 microglobulin in 11 cases, the low levels, could be explicated because the patients were in early stage and not previous treatment. CR was achieved in 112 (88%) cases; 60 were allocated to received maintenance and 62 in control group. Actuarial curves at 10-years progression-free survival was 85% (95% Confidence interval 78% - 93%(95%CI) in patients whose received maintenance was better compared with patients whose did nor received maintenance :54% (95% CI :48-59%) (p < 001). Overall survival (OS) was 87 % (95%CI: 82% - 94 %) and 53% (95%CI: 47% - 61%) respectively, (p < 001) Toxicities were minimal, during chemotherapy administration granulocytopenia grade 2 in 56 cases in 172 cycles ((5%), and 82 cases with grade 1 (7.3%), grades, > 2 infection related granulocytopenia or dead=related treatment were observed. Minimal neurological toxicities were observed during maintenance, but, it were necessary to delay or modified doses of thalidomide. Until now, no late toxicities has been observed.

Table 1: Demoghrafic characteristics.

At diagnosis	No (%)	CR (%)	Maintenance (%)	
			Yes	Not
	126 (100)	112 (88)	60 (44.2)	62 (55.0)
Male	74 (58.7)	67(59.8)	29(48.3)	32 (51.6)
Female	52 (41.0)	45 (40.0)	29 (48)	30 (48.3)
Age (years) range	57 -78	50 – 36	47 – 76	56 -78
Median	63.8	67.6	64.8	63 -72)
Stage IIA	48 (38.5)	39 (81.5)	30 (50.0)	30 (48.)
IIIA	78 (66.3)	30 (50)	30 (48.8)	(32 (56.6)

Discussion

MF is the most common clinical presentation of cutaneous T-cell lymphomas, generally is present in younger patients, and most males. The disease have a pleomorphic clinical presentation, according to the time of evolution, more of the patients has been treated as cutaneous lesions, and when the topical presentation did not response, biopsies are taking, that stablish the correct diagnosis, but at this time of course the disease has clinical advances, and > 20 % have visceral involvement. Even with a diagnosis of MF, most treatments were non-aggressive , with single biological modifiers or single chemotherapy, of course CR is observed in < 20%, with a relative short time to MF show progression. At this time, multiple studies has been conducted with CR between 15 % to 26 %, and poor outcomes [11] It is appear that MF did not represent a neoplasms that need aggressive treatment, but, continuous relapses, worsening the feel of the patient, thus when need an aggressive chemotherapy, anxiety and fear is common. Thus, we development with an gemcitabine -based therapy, because gemcitabine has been to be effective in T-cell lymphomas, and NK-T nasal lymphoma, and etoposide and methotrexate that pharmacokinetics studies were observed are effectives in T-cell lymphomas [12].

Taking in consideration, that MF present early relapse, it is indication that tumor cells remain active. Maintenance in patients with hematological malignancies has been employed in some, with different results. Immunomodulators has been employed with improve outcomes in T-cell lymphomas, but, lenalidomide is associated with severe toxicities: severe granulocytopenia, infection, special viral infections, and in multiple myeloma has been associated with 30 % of second neoplasm, thus, lenalidomide it is not recommend. Thalidomide is an immunomodulator, with middle toxicities, general neurological, well controlled. In the present study, we show that an moderate aggressive chemotherapy, based in drugs that have show clinical activity in T-cell neoplasms increase CR, and low doses of thalidomide increase PFS and OS. > 75 % of patients remain in first CR, and > 85 % are alive at a median follow-up.

The use of granulocyte colony factor reduce the risk of infections, and the use of thalidomide did no need stopped or delay treatment were not necessary Recently has been approved multiples new drugs for the treatment of relapsing MF, but, results did not appear to increase significantly PFS and OS [13]. The addition to maintenance therapy in MF, could be considered experimental, we found, only a report that employed maintenance therapy in MF patients at CR after radiation therapy [14]. Ofcourse is necessary more studies with these end-point, to define that at a moderate aggressive chemotherapy regimen, and principally evaluated the benefit of thalidomide as maintenance drug.

Conflict of Interest

Both authors disclose any conflict of interest. The work did not receive external support, and was performed with the owner resources of the Instituto Mexicano del Seguro Social.

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