Other Chemotherapeutic Agents in Cutaneous T-Cell Lymphoma

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KEYWORDS

• Chemotherapy • Response rate • Clinical trial

KEY POINTS

- Traditional chemotherapies are used throughout the world in the treatment of cutaneous T-cell lymphoma (CTCL).
- Both single and multiagent chemotherapies can benefit patients with CTCL.
- There currently are no data to support the use of traditional chemotherapies over other therapies for CTCL. Therefore, in patients with less advanced disease, alternative therapies should be considered.

INTRODUCTION

Currently, no traditional chemotherapy agents are Food and Drug Administration (FDA) approved for the treatment of mycosis fungoides (MF) or Sézary syndrome (SS). Multiple chemotherapeutic treatments for MF and SS, such as systemic nitrogen mustard and multiagent chemotherapy regimens (eg, cyclophosphamide, adriamycin, vincristine, and prednisone [CHOP]), were initially used because of established activity in other non-Hodgkin lymphomas (NHLs) or Hodgkin lymphomas. Over time, specific treatments were reported by astute physicians to be particularly effective in MF/SS, such as the Winkelmann chlorambucil regimen. More recently, however, it has been recognized that some of these regimens, which are often characterized by significant immunosuppression and toxicity, are not more effective than agents described elsewhere in this issue (eg, interferons [IFNs]).[1] Nevertheless, these other "chemotherapeutic" agents remain an important therapy option for some patients with MF/SS. This article describes those chemotherapeutic agents not discussed elsewhere in this issue with a review of the data supporting their use. **Table 1** summarizes single-agent therapies in MF/SS and **Table 2** summarizes multiagent chemotherapies. Readers are further referred to a comprehensive review on the treatments used for SS and MF by Olsen and colleagues[2] for additional in-depth discussion of many of the agents discussed later.

ANTIMETABOLITES

Antimetabolites are typically low-molecular-weight molecules with structures resembling normal cellular constituents that act by disrupting normal metabolic pathways. There are 3 common subgroups: (1) purine analogs, (2) pyrimidine analogs, and (3) folates.

Purine Analogs/Antagonists

Purine analogs are antimetabolites with a chemical structure that mimics the purine bases (adenine and guanine) and interferes with DNA polymerase

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Table 1
Summary of single-agent and combination chemotherapy studies in the treatment of mycosis fungoides or Sézary syndrome

Agent(s)	Response Rate (Responders/Total)	Dosing	Study
Fludarabine	2/5	25 mg/m^2 × 5 d, q3–4 wk	Redman et al,[4] 1992
	6/31	18–25 mg/m^2 × 5 d, q4 wk	Von Hoff et al,[5] 1990
Fludarabine + ECP	7/27 MF; 6/17 SS	25 mg/m^2 × 5 d, q4 wk	Quaglino et al,[6] 2000
Fludarabine + IFN	18/35	25 mg/m^2 × 5 d q4 wk; 5 million units, TIW	Foss et al,[7] 1994
Fludarabine + cyclophosphamide	5/6	18 mg/m^2 × 3 d, q4wk; 250 mg/m^2 × 3 d, q4wk	Scarisbrick et al,[8] 2011
Cladribine	2/2	0.1 mg/kg × 7 d, q4wk	Betticher et al,[9] 1994
	2/9	4 mg/m^2 × 7 d, q4wk	O'Brien et al,[10] 1994
	9/22	0.1 mg/kg × 5–7 d, q4wk	Kuzel et al,[11] 1996
	2/8	0.06 mg/kg × 5 d, q4wk	Trautinger et al,[12] 1999
Pentostatin	10/32	3.75–5 mg/m^2 × 3 d, q3wk	Tsimberidou et al,[14] 2004
	4/8	5 mg/m^2 × 3 d, q3wk	Cummings et al,[15] 1991
	7/18	Varied	Greiner et al,[17] 1997
	5/22 MF; 7/21 SS	4 mg/m^2 q1–4wk	Ho et al,[18] 1999
	4/6 MF; 10/14 SS	5 mg/m^2 × 3 d, q3wk ± 1.25 mg/m^2 on subsequent cycles	Kurzrock et al,[19] 1999
Pentostatin, cyclophosphamide, and bexarotene	5/5 MF; 2/3 SS	4 mg/m^2 q2wk; 600 mg/m^2 q2wk; 300 mg/m^2 qd × 8 mo	Calderon Cabrera et al,[21] 2013
Pentostatin + IFN	17/41	4 mg/m^2 × 3 d	Foss et al,[20] 1992
Gemcitabine	9/19	1200 mg/m^2 d 1, 8, 15, and 28	Zinzani et al,[144] 2010
	19/26 MF; 0/1 SS	1200 mg/m^2 d 1, 8, 15, and 28	Marchi et al,[29] 2005
	21/30	1000 mg/m^2 d 1, 8, and 15	Duvic et al,[30] 2006
	3/3	1000 mg/m^2 d 1, 8, and 15 then 250 mg/m^2 weekly	Buhl et al,[32] 2009
	7/9 MF; 2/4 SS	1000 mg/m^2 d 1 and 8 of a 21-d cycle or d 1, 8, ± 15 of a 28-d cycle	Jidar et al,[31] 2009
Mechlorethamine	34/41	Varied	Van Scott et al,[37] 1975
Chlorambucil + prednisone	23/26 (all SS)	2–6 mg/d; 20 mg/d	Winkelmann et al,[44] 1984
	6/6	2–6 mg/d; 5–20 mg/d	Hamminga et al,[42] 1979
Chlorambucil + fluocortolone	13/13	Clorambucil 10–12 mg/d × 3 d; fluocortolone 75 mg d 1, 50 mg d 2, 25 mg d 3	Coors & von den Driesch,[43] 2000

Chlorambucil + prednisone + leukapheresis	11/11	4 mg/d; 20 mg/d; Leukapheresis 2–3 × per wk	Winkelmann et al,[44] 1984
Bendamustine	2/3	60–100 mg/m^2	Zaja et al,[59] 2013
Cyclophsphamide	4/4	Varied: 200–700 mg/d	Abele & Dobson,[61] 1960
	5/11	Varied: 50–300 mg/d	Van Scott et al,[66] 1962
TMZ	3/9	150 mg/m^2/d × 5 d, q4wk, Then 200 mg/m^2/d × 5 d q4wk	Tani et al,[75] 2005
	7/26	200 mg/m^2/d PO × 5 d q4wk	Querfeld et al,[76] 2011
Liposomal daunorubicin	3/3	20–40 mg/m^2 q3–4wk	Wollina et al,[92] 2003
Doxorubicin	7/13	60 mg/m^2 q3wk	Levi et al,[84] 1977
	26/30 MF; 1/1 SS	20–40 mg/m^2 q2–4wk	Wollina et al,[85] 2003
	3/10	20 mg/m^2 q4wk	Di Lorenzo et al,[86] 2005
	12/13 MF; 1/3 SS;	20 mg/m^2 q4wk	Pulini et al,[87] 2007
	6/10 MF; 3/5 SS	40 mg/m^2 q4wk	Quereux et al,[88] 2008
	20/49	20 mg/m^2 q2wk	Dummer et al,[89] 2012
Doxorubicin + bexarotene	14/34 (Doxorubicin only); 7/15 (doxorubicin + bexarotene)	Doxil 20 mg/m^2 q2wk; bexarotene 300 mg/m^2/d	Straus et al,[90] 2014
Etoposide ± cyclophosphamide	2/5 (Etoposide only); 3/4 (etoposide + cyclophosphamide)	100 mg/m^2 IV × 5 d, q2–3wk ± cyclophosphamide	Molin et al,[99] 1979
IL-2	3/3 MF; 1/3 SS	20 million units/m^2 on d 1–5, 14–17, and 28–30 (induction) followed by 2 d/mo for 5 mo (consolidation)	Baccard et al,[111] 1997
	5/7	20 million units/m^2/d for 5, 4, and 3 d (wk 1, 3, and 5) followed by optional monthly maintenance × 5 d	Gisselbrecht et al,[112] 1994
	4/22	20 million units/m^2/d on d 1–4 × 6 wk in an 8-wk cycle	Querfeld et al,[107] 2007
IL-12	5/10	50, 100, or 300 ng/kg twice weekly, up to 24 wk	Rook et al,[117] 1999
	10/23	100 ng/kg twice weekly × 2 wk then 300 mg/kg twice weekly through 24 wk	Rook et al,[118] 2001
Forodesine	9/13	40–320 mg/m^2 BID × 4 d in a 16-d cycle	Lansigan & Foss,[127] 2010
	10/37 (MF/SS + other T-cell lymphomas)	40–320 mg/m^2/d × 4 wk	Duvic et al,[128] 2006
	11/101	200 mg daily (approximately 80 mg/m^2)	Dummer et al,[129] 2014
Bortezomib	7/10	1.3 mg/m^2 twice weekly × 2 wk in a 3-wk cycle	Zinzani et al,[133] 2007

Abbreviation: TIW, three times weekly.

Table 2
Combination chemotherapy used in the treatment of mycosis fungoides/Sézary syndrome

Therapy Regimen	No. of Patients	Complete Response + Partia Response, *n* (%)	Complete Response, *n* (%)	Median Duration of Response (mo)	Stage	Reference
MOPP/COPP + TSEB	21	19 (70)	11 (52)	14	I–III	Hallahan et al,[145] 1988; Bunn et al,[146] 1994
BLM + MTX	10	9 (90)	1 (10)	6	T3	Groth et al,[147] 1979
CHOP/HOP	12	10 (83)	5 (42)	5	II–IV	Grozea et al,[148] 1979; Lamberg et al,[149] 1979
CHOP/COP	30	9 (30)	3 (10)	6	Not reported	Fierro et al,[150] 1998
CHOP	1	0	0	—	T3	Molin et al,[151] 1980; Raafat & Oster,[152] 1980
CVP	4	3 (75)	1 (25)	Not reported	IV	Lutzner et al,[153] 1975
CVP	3	2 (67)	0 (0)	Not reported	T3	Molin et al,[151] 1980; Raafat & Oster,[152] 1980
CVP	16	8 (50)	4 (25)	12	IIB (4), III (1), IV (11)	Tirelli et al,[154] 1986
CVP ± TSEB	12	6 (50)	4 (33)	Not reported	III	Hamminga et al,[155] 1982
CBP	8	5 (63)	2 (25)	Not reported	Not reported	Molin et al,[156] 1987
CBP + retinoid	12	7 (58)	3 (25)	Not reported	Not reported	Molin et al,[156] 1987
CBP + retinoid	20	18 (90)	16 (80)	8	—	Zachariae & Thestrup-Pedersen,[157] 1987
CBP + retinoid + TF	10	8 (80)	8 (80)	Not reported	—	Zachariae et al,[158] 1987
CAVOP	5	4 (80)	1 (20)	Not reported	T3	Molin et al,[151] 1980; Raafat & Oster,[152] 1980
COP + BLM	12	11 (92)	2 (17)	11.5	II–IV	Grozea et al,[148] 1979; Lamberg et al,[149] 1979
VICOP-B	25[a]	(84)	(36)[a]	8.7	IIB and IV	Fierro et al,[96] 1997
EPOCH	15	12 (80)	4 (27)	8	IIB–IVB	Akpek et al,[159] 1999
Cyclophosphamide + VP-16	4	3 (75)	1 (25)	6	Various, majority T3	Molin et al,[99] 1979
MBPE	11	8 (73)	1 (9)	6	II–IV	Doberauer & Ohl,[160] 1989
CAVE	52	47 (90)	20 (38)	Not reported	II–IV	Kaye et al,[161] 1989
TSEB + doxorubicin + cyclophosphamide	50	49 (98)	44 (88)	Range 2–75	I (20); II (20); III (7); IV (3)	Braverman et al,[162] 1987
BAM	10	8 (80)	7 (70)	41	IIB–IVB	Zakem et al,[163] 1986

Abbreviations: BAM, bleomycin, adriamycin, and MTX; BLM, bleomycin; BVP, bleomycin, vinblastine, and prednisone; CAVE, cyclophosphamide, adriamycin, vincristine, and etoposide; CAVOP, cyclophosphamide, adriamycin, vincristine, VP-16, and prednisone; CBP, cyclophosphamide, bleomycin, and prednisone; COMP, cyclophosphamide, vincristine, MTX, and prednisone; COP/CVP, cyclophosphamide, vincristine, and prednisone; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; MBPE, MTX, bleomycin, prednisone, and etoposide; MOPP, meclorethamine, vincristine, procarbazine, and prednisone; TF, transfer factor; TSEB, total skin electron beam therapy.

[a] Includes a cohort of patients with pleomorphic lymphoma.

and ribonucleotide reductase, thus inhibiting both DNA and RNA synthesis. It is unclear which of these play a more important role in cytotoxicity, or if both do.

6-Mercaptopurine

6-Mercaptopurine (6-MP or Purinethol) is an oral thiopurine used in acute lymphocytic leukemia. It has not been studied in MF/SS and is not recommended in the National Comprehensive Cancer Network (NCCN) guidelines for NHL.[3]

Fludarabine

Fludarabine (Fludara) is an adenosine analog that inhibits adenosine deaminase, leading to an accumulation of deoxyadenosine triphosphate, which in turn inhibits DNA polymerase and ribonucleotide reductase. It can be given both orally (available in Canada but not in the United States) and intravenously (IV). It is FDA approved for use in chronic lymphocytic leukemia (CLL) and is also used as a component of multiagent chemotherapy for NHL. As a single agent, fludarabine at 18 to 25 mg/m^2 for 5 days every 3 to 4 weeks was modestly effective in advanced-staged MF with an overall response rate (ORR) of 26% (21/80 patients) between three trials [2/5 (40%)] of patients with MF (Redman and colleagues[4]), stage not otherwise reported; 6/31 (19%) evaluable patients with stage IB–IVB MF (Von Hoff and colleagues)[5]; and 13/44 (29.5%) patients with stage IIB–IV MF (Quaglino and colleagues).[6] Fludarabine has been used in combination with IFN (5–7.5 million units/m^2 3 times a week)[7] in 35 patients with MF, 31 who had stage IV disease, with an ORR of 51%. Fludarabine has also been used in combination with cyclophosphamide (250 mg/m^2 $\times$ 3 days every 4 weeks $\times$ 3–6 months)[8] in 12 patients with stage III–IVA MF/SS, with an ORR of 42%. The duration of response was low.

Given its modest benefit and significant side effects of myelosuppression and immunosuppression with lymphocyte dysfunction that persists beyond treatment, fludarabine has a limited role in the treatment of MF/SS outside of its role in conditioning regimens for stem cell transplant. Additional side effects include dose-dependent neurotoxicity, gastrointestinal (GI) symptoms, and pulmonary toxicity.[2] Secondary neoplasms have also been reported.

Cladribine

Similar to fludarabine, cladribine (2-chlorodeoxyadenosine, 2-CdA, or Leustatin) is an adenosine analog that inhibits DNA and RNA synthesis through its interaction with adenosine deaminase. Due to the high concentration of adenosine deaminase in T lymphocytes, cladribine acts preferentially in this cell population. It is FDA approved for hairy cell leukemia. In 1 of several early studies, 2 of 2 patients (stages not reported) treated with cladribine, 0.1 mg/kg/d for 7 days every 4 weeks, had a partial response (PR).[9] O'Brien reported on a complete response (CR) in 1/8 patients with stage I–IV MF treated with cladribine, 4 mg/m^2/d for 7 days every 28 days.[10] Kuzel and colleagues[11] performed a phase II study examining 0.1 mg/kg/d for 5 to 7 days and reported an ORR of 28%, including 3 with a CR (3/4 stage IB, 0/2 stage IIB, 2/5 stage III, 1/8 stage IVA, and 0/2 stage IVB). Low-dose cladribine, 0.06 mg/kg/d $\times$ 5 days every 4 weeks for up to 8 cycles, has been shown to provide some palliation (1/2 stage IIB and 1/6 stage IVA ORR).[12]

Similar to fludarabine, cladribine causes myelosuppression and protracted lymphopenia, with a decrease in CD4/CD8 ratio that can last 6 to 9 months after treatment.[2] Given the high degree of immunosuppression associated with advanced MF/SS,[13] this side effect limits the use of cladribine in MF/SS.

Pentostatin

Pentostatin (deoxycoformycin or Nipent) also inhibits adenosine deaminase, leading to a block in DNA synthesis. It is FDA approved for use in hairy cell leukemia. In one of the larger studies to examine pentostatin in advanced-stage (IIB or higher) disease, there was an ORR of 56% among 32 patients.[14] Dosing was 5 mg/m^2 for 3 days every 3 weeks. In an Eastern Cooperative Oncology Group (ECOG) study of 8 patients with CTCL (stages not reported), 4 of 8 had a response.[15] Dang-Vu and colleagues[16] reported on 1 patient with stage IIA MF treated with 5 mg/m^2/d for 3 days repeated at 35- to 71-day intervals who had a CR that lasted greater than 16 months off therapy. In a study by Greiner and colleagues[17] in 18 patients with stage I–IVB using 4 to 5 mg/m^2 every 1 to 4 weeks, there was an ORR of 39% (0/1 stage IA, 3/4 stage IIA, 1/3 stage IIB, 1/3 stage III, 2/6 stage IVA, and 0/1 stage IVB), including 2 CRs, with a median number of 5 cycles. In a study performed by the European Organisation for Research and Treatment of Cancer (EORTC), 22 patients with MF with lymphadenopathy or organomegaly and 21 patients with SS treated with pentostatin demonstrated 23% (5/22 patients) and 33% (7/21 patients) ORR, respectively.[18] Dosing in this trial was 4 mg/m^2 weekly for 3 weeks followed by every other week for 6 weeks. There was a monthly maintenance phase for 6 additional months at 4 mg/m^2. In a dose-adaptable study with a starting dose of 5 mg/m^2, Kurzrock and colleagues.[19] reported a response

in 70% of 20 patients (10/14 SS and 4/6 tumor stage). Pentostatin (days 1 and 3 at 4 mg/m^2) has been combined with IFN (days 22 and 50 at 10 million units/m^2 and days 23 through 26 at 50 million units/m^2) in a phase II study of 41 patients (2 stage I–IIA, 5 stage IIB/III, 27 stage IVA, and 7 stage IVB) that showed an ORR of 41%.[20] Response in the blood, as defined by at least a 50% reduction in circulating atypical cells, was seen in 8 of 24 patients with blood involvement. None of the 7 patients with IVB (visceral involvement) had a response.

One retrospective study of 8 patients examined the use of pentostatin (4 mg/m^2 every 2 weeks) plus bexarotene (150 mg/m^2 $\times$ 14 days followed by 300 mg/m^2 $\times$ 14 days) plus cyclophosphamide (600 mg/m^2 every 2 weeks) for up to 8 cycles.[21] A median of 4 cycles was completed, with only 3 patients completing all 8 cycles. The response rate was 88% (1/1 stage IIA, 1/1 stage IIB, 2/2 stage III, 1/1 stage IVA, and 2/3 stage IVB); 5 patients demonstrated a CR, including the 2 patients with stage IVB. Unlike many prospective trials in MF/SS, however, most patients in this study had not been heavily pretreated (or were entirely treatment naïve).

Pentostatin can cause hematologic side effects, including a prolonged depression of CD4 count.[2] The bone marrow suppression with pentostatin typically occurs, however, in the initial cycles and is not as prolonged as observed with other adenosine deaminase inhibitors. GI distress, fevers, and transient liver function test abnormalities may also occur. Neurologic and pulmonary side effects have also been reported.[2]

Pyrimidine Analogs/Antagonists

Pyrimidine analogs are antimetabolites with a chemical structure that mimics pyrimidine bases (uracil and cytosine). Both DNA and RNA synthesis are inhibited, although similar to the purine analogs, it is uncertain which mechanism is most important in cytotoxicity and cell death.

5-Fluorouracil

5-Fluorouracil (5-FU or Adrucil) is an antimetabolite that mimics uracil and inhibits DNA synthesis through irreversible inhibition of thymidylate synthase.[22] There are few data on the use of IV 5-FU in the treatment of lymphoma. One study of 10 patients (1 stage IIA, 4 stage IIB, 1 stage III, 2 stage IVA, and 2 stage IVB) who were treated sequentially with methotrexate (MTX) (60–120 mg/m^2) followed by 5-FU (20 mg/kg per 24 hours for 36 hours) and leucovorin showed response in all patients treated.[23] The median survival for patients with tumors, regardless of stage, in this study was 5.25 years, compared with 3.3 years for patients not treated with this regimen.[24] There has been little follow-up, however, regarding these preliminary findings.

In a similar fashion, topical 5-FU has been reported to be of benefit in some patients with MF. Zackheim and Farber[25] considered the use of topical antimetabolites for the treatment of skin lymphoma more than 40 years ago. Only 1 trial with 6 patients (4 stage IA, 1 stage IB, and 1 stage IIB) has examined the use of topical 5-FU in MF/SS thus far. After daily topical treatment with 5-FU for 3 to 18 months, all 6 patients demonstrated a response.[26]

Cytosine arabinoside

Although there are data supporting the use of cytosine arabinoside (cytarabine or ara-C) in some NHLs, there are no data supporting its use in MF/SS. It is not recommended in the NCCN guidelines for treatment of CTCL.

Gemcitabine

Gemcitabine (2′,2’-difluorodeoxycytidine or Gemzar) is a pyrimidine nucleoside analog that mimics deoxycytidine. It is phosphorylated intracellularly and inhibits DNA synthesis. Gemcitabine is unique among the pyrimidine analogs in that it inhibits its own deamination (through interference of deoxycytidylate deaminase), thereby prolonging its activity.[27] It is FDA approved for use in breast, ovarian, lung, and pancreatic cancer. In a phase II study of 30 patients with stage T3 or T4,N0,M0 MF who had failed previous systemic therapy and were treated with 1200 mg/m^2 days 1, 8, and 15 monthly $\times$ 3 months, there was a 70% response rate.[28] In a follow-up from 1 of the centers in this study, Zinzani and colleagues reported on 19 patients with T3 or T4,N0,M0 MF who were followed for up to 10 years after treatment with gemcitabine (3–6 cycles at 1200 mg/m^2/d on days 1, 8, and 15 of a 28-day cycle). There was an ORR of 48% with a disease-free interval of 10, 18, and 120 months in 3 patients with a CR. In a multicenter phase II study of 26 patients with untreated MF/SS with advanced-stage disease (T3 or T4,N0,M0) treated with gemcitabine at 1200 mg/m^2 on days 1, 8, and 15 of a 28-day cycle for 6 cycles, an ORR of 73% was observed.[29] There was 1 patient in this trial with SS and that patient did not have a response.[29]

In another phase II study of gemcitabine in patients with MF, primarily stage IIB or greater, treated with 1000 mg/m^2 on days 1, 5, and 8 of a 28-day cycle, 20 of 31 (65%) had a response. Among those patients with stage IVA and IVB having B2 blood involvement (SS), 8 of 11

patients responded.[30] A retrospective study of 14 patients with MF with T3 or T4 disease (11 were transformed) and 6 patients with SS at 4 centers treated with 1000 mg/m^2 (with various schedules) showed 78% ORR in MF and 50% ORR in SS.[31] In a separate study, 3 patients with refractory tumor-stage MF demonstrated a response to gemcitabine, administered at 1000 mg/m^2 for multiple cycles, which was then decreased to 250 mg/m^2 weekly.[32] In all 3 patients, there was eventual progression of lymphoma within 4 months of stopping therapy (including 1 case with meningeal involvement), suggesting that low-dose gemcitabine is not useful as a maintenance therapy. These findings are in contrast to a separate case series reporting that 4 of 8 patients with refractory MF who had a response with lower-dose gemcitabine (150 mg/m^2).[30] The role of lower-dose gemcitabine in maintenance therapy requires further exploration. Finally, in a trial that combined gemcitabine, 1000 mg/m^2 IV on days 1 and 8 of a 21-day cycle for 4 cycles, with bexarotene, 300 mg/m^2 daily in 35 patients with MF/SS (5 stage IB, 2 stage IIA, 8 stage IIB, 8 stage III, and 12 stage IVA), the combination was not superior to gemcitabine alone.[33]

More common side effects of gemcitabine include elevations in liver function tests and bone marrow suppression with anemia, thrombocytopenia, and/or leukopenia. Other side effects include pulmonary toxicity, hemolytic uremic syndrome, exacerbation of radiation toxicity, capillary leak syndrome, hyperpigmentation, and posterior reversible encephalopathy,[2,34] all of which are rare.

Antifolates

Pralatrexate and MTX are discussed in the article by Wood and Wu elsewhere in this issue.

ALKYLATING AGENTS

Alkylating agents in chemotherapy were developed after it was noted that people exposed to the military agent, mustard gas, developed bone marrow suppression and lymphopenia. Nitrogen mustard was a less toxic agent that showed efficacy in various lymphomas.[35] There are 6 types of alkylating agents: (1) nitrogen mustards, (2) nitrosoureas, (3) alkyl sulfonates, (4) triazines, (5) ethylenimines, and (6) metal salts. The cellular enzyme O^6-methylguanine–DNA methyltransferase (MGMT) is able to repair the cytotoxic damage caused by alkylating agents, thereby introducing a mechanism for resistance to these compounds.

Nitrogen Mustards

Mechlorethamine

Mechlorethamine (Mustargen) is an alkylating agent that is currently infrequently used in a systemic form in the treatment of MF and SS. Karnofsky[36] and Van Scott and colleagues[37] reported 21 and 41 cases of MF/SS, respectively, treated with systemic nitrogen mustard. Karnofsky noted some benefit in the first cycle but later cycles were less effective.[36] Van Scott treated 46 patients with advanced cutaneous lymphomas, including 41 with MF or SS, with systemic Mustargen at various dosing regimens along with topical nitrogen mustard and reported a decrease in stage of disease in 34/41 MF/SS patients, including 12/41 (29%) with a CR.[37] These results with systemic nitrogen mustard ultimately led to the use of topical nitrogen mustard in the treatment of MF/SS.

Lymphopenia due to systemic mechlorethamine is common. Additional side effects include alopecia, tinnitus, nausea, vomiting, hypersensitivity, skin eruptions, and damage to reproductive organs/infertility. Thrombosis and thrombophlebitis may occur when the drug is infused IV.

Chlorambucil

Developed from nitrogen mustard, chlorambucil (Leukeran) is an alkylating agent that prevents DNA replication by cross-linking DNA, leading to DNA strand breaks. Chlorambucil was one of the first systemic treatments recognized to have activity specifically in SS[38,39] and since that time, there have been multiple case reports/series suggesting benefit in this setting.[40–42] Winkelmann developed the Winkelmann method, which consists of oral chlorambucil (2–6 mg/d) with prednisone (10–20 mg/d, weaned over time) for the treatment of SS.[39,43–45] It has also been adapted for the treatment of CLL, where it continues to be a common therapy.[45] Winkelmann reported that SS patients lived twice as long with chlorambucil therapy and 10 of 17 patients had a decreased peripheral blood Sézary cell count. Seven of 19 SS patients had a CR for at least 1 year on chlorambucil/corticosteroid.[44] Coors and colleagues[43] used chlorambucil with corticosteroids (chlorambucil 10–12 mg for 3 days and fluocortolone, first day 75 mg, second day 50 mg, and third day 25 mg) twice monthly and reported a 100% ORR in 13 patients with erythrodermic disease (8 stage III, 4 stage IVA, and 1 stage IVB). Moreover, a significant improvement in pruritus was also reported. McEvoy and colleagues[46] described 11 patients treated with combined chlorambucil-prednisone using the

Winkelmann method and adding leukapheresis with an ORR of 100%.

Lower doses of chlorambucil as utilized in the Winkelmann method are well tolerated. Leukopenia can occur and requires monthly blood counts.[2] Less common side effects include bone marrow suppression (thrombocytopenia, anemia, and leukopenia), drug fever, and hyperuricemia, which often occur soon after starting therapy. Additionally, because some patients remain on chlorambucil for longer periods of time, it is important to be aware of the delayed side effects, which include amenorrhea, azospermia, infertility, pulmonary interstitial fibrosis, cystitis, hepatotoxicity, and peripheral neuropathy. These toxicities are consistent among other alkylating agents. Although in a past, study doses above 1300 mg of chlorambucil were found leukomogenic,[47] more recently the risk of secondary malignancy in NHL after chlorambucil treatment was not found significant.[48]

Ifosfamide

Ifosfamide is an alkylating agent that has been combined with other chemotherapies in the treatment of NHL. It is part of ifosfamide, carboplatin, and etoposide (ICE) and ifosfamide and etoposide (IFE) multiagent chemotherapy. Although there are no data on its use in MF/SS, it has been reported (multiagent ICE regimen) in the treatment of non-MF CTCL.[49] It is also used as a second-line agent for aggressive T-cell lymphomas.[50]

Bendamustine

Bendamustine (Treanda) is a nitrogen mustard alkylating agent. Its chemical structure also makes it a purine analog.[51] This diversity in structure may explain why it is effective in a diverse range of cancers, including CLL[52]; multiple myeloma[53]; solid tumors, including breast and lung cancer[54,55]; and NHL.[56,57] It has a different antitumor effect than other alkylating agents (including cyclophosphamide, chlorambucil, or melphalan) and seems to function not only as an alkylating agent causing DNA breaks but also through effects on transcription and posttranslational events.[51] Bendamustine's structure and diversity of mechanism of action may make it less susceptible to drug resistance than other alkylating agents.[51] It is FDA approved for the treatment of indolent NHLs and CLL. Bendamustine, 120 mg/m^2/d over 30 to 60 minutes on days 1 and 2 every 3 weeks, for a total of 6 cycles, demonstrated benefit in T-cell lymphomas in an early phase II trial. This trial only included 2 MF patients (stage not defined) who were not analyzed as a subgroup. The ORR in the study (with most patients having peripheral T-cell lymphoma [PTCL]) was 50% (30 of 60 patients).[58] In a second trial that enrolled 3 patients with advanced-stage MF/SS, there were 2 with a PR at monotherapy doses of 60 to 100 mg/m^2.[59] The nonresponder, however, only received 1 cycle of bendamustine.

Myelosuppression requiring granulocyte colony-stimulating growth factors frequently occurs. Other hematologic abnormalities are also common, including lymphopenia, anemia, and thrombocytopenia. Infections, infusion reactions, and severe skin reactions, including toxic epidermal necrosis, have been reported. There are also reports of severe cytomegalovirus reactivation with treatment.[60] The most common nonhematologic side effects are nausea and vomiting.

Cyclophosphamide

Cyclophosphamide (Cytoxan) is an alkylating agent and derivative of mechlorethamine. Similar to other alkylating agents, it induces double-strand breaks in DNA. Although multiple studies have shown that single-agent cyclophosphamide has activity against MF/SS, the benefit is often low.[61–66] Abele and Dobson[61] reported 4 cases, mostly with early-stage disease, who showed a response. Van Scott and colleagues[66] subsequently reported 11 more cases, with 5 patients responding to single-agent cyclophosphamide at 50 to 300 mg/d for up to 117 days. Patients were treated until they developed leukopenia or anemia. There are multiple dose-limiting toxicities. Hemorrhagic cystitis, risk to reproductive capacity, and total alopecia are additional issues. Currently, single-agent cyclophosphamide is uncommonly used. As part of multiagent regimens (eg, CHOP), it remains a commonly used drug in MF/SS (see **Table 2**).

Melphalan

Melphalan (phenylalanine mustard, L-PAM, or Alkeran) is an alkylating agent and not used in the primary treatment of MF/SS but is used in combination in some conditioning regimens during stem cell transplantation.[67–69] This is discussed in the article by Virmani and colleagues elsewhere in this issue.

Lomustine

Lomustine (CeeNU) is an alkylating agent that is approved by the FDA for the treatment of brain tumors and Hodgkin lymphoma. It has not been studied in MF/SS but has been reported to have activity in 2 Tasmanian devils, 1 ground cuscus, and frequently in dogs with CTCL.[70–72] It is not recommended in the NCCN guidelines for treatment of NHL.

Nimustine

Similar to carmustine (BCNU), nimustine (ACNU or Nidran) has activity against MF, although the level of activity has been relatively undefined. It is not FDA approved for any use.[73]

Nitrosoureas

Carmustine

Carmustine is used IV for some lymphomas but not for MF/SS. It is compounded for topical application.

Alkyl Sulfonates

Busulfan

Busulfan (Busulfex or Myleran) is not used in the primary treatment of MF/SS but is used in combination in some conditioning regimens during stem cell transplantation.[67–69]

Triazines

Dacarbazine

Dacarbazine (DTIC or DTIC-Dome) is an alkylating agent that is not used as a single agent in MF/SS but is part of the doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD) multiagent chemotherapy, a first-line therapy for Hodgkin lymphoma. Its benefit in MF/SS has not been established.

Temozolomide

Temozolomide (TMZ or Temodar) is an oral alkylating agent and a derivative of dacarbazine that is FDA approved for the treatment of certain brain cancers. In several small studies it has been shown to have activity in MF/SS. One patient with advanced MF was part of a study of 42 patients examining TMZ therapy for advanced cancer. The patient had a CR that lasted 7 months.[74] In a study of 9 patients with stage IIB or III MF, there was an ORR of 33% (3 of 9).[75] In the most recent trial, which examined TMZ at 200 mg/m^2 for 5 days every 28 days in stage IB–IVA MF/SS, there was an ORR in 7 of 26 (27%) in patients with treatment refractory disease.[76] Response was assessed at the 2nd cycle and responders were treated with TMZ through 1 year. The median disease-free survival, however, was only 4 months.

Myelopsuppression is common and requires dose reduction. The drop in neutrophils commonly occurs on day 22 after the initial dose. Nausea, vomiting, hepatotoxicity, and infections can also occur. Prophylaxis for pneumocystis pneumonia is required.

Procarbazine

Procarbazine (Matulane) has not been reported in the primary treatment of MF/SS but is used in certain multiagent regimens, such as MOPP (see **Table 2**).

Ethylenimines

Thiotepa

Thiotepa (Thioplex) is not used in the primary treatment of MF/SS but is used in combination in some conditioning regimens during stem cell transplantation.[67–69]

Metal Salts

Carboplatin

Carboplatin (Paraplatin) is not used in the primary treatment of MF/SS but is used in multiagent ICE therapy. ICE is generally reserved, however, for use only in transformed MF/SS as a second-line therapy.[50]

Cisplatin

Cisplatin (Platinol) is not used in the primary treatment of MF/SS but is used in multiagent (eg, etoposide, methyprednisilone, cytarabine, cisplatin [ESHAP]) therapy. ESHAP is generally reserved, however, for use only in second- or third-line salvage therapy in transformed MF/SS. Moreover, its risk/benefit has been questioned by a past study in patients with aggressive CTCL, which included 1 SS and 1 MF patient, due to high recurrence and low duration of response.[77] There was 1 PR in the MF patient, but that patient demonstrated disease progression within 2 months.

TOPOISOMERASE INHIBITORS

Anthracyclines

Anthracyclines were first developed from a compound found in the soil bacteria *Streptomyces*.[78] They are 1 of the most important class of drugs in the treatment of hematologic cancers[79] and work mainly by DNA intercalation and inhibition of topoisomerase II.[80] Although there is a strong antitumor effect, cardiotoxicity has been a common side effect that has historically limited use. Newer delivery systems that involve liposome encapsulation prolong the half-life of drug in circulation and alter the biodistribution such that there is increased deposition in tumor tissue with decreased deposition in normal tissues, with resultant decreased toxicity.[81–83] Pegylation additionally improves pharmacodynamics and pharmacokinetics of the drug. These formulations with decreased cardiotoxicity have allowed anthracyclines to be important agents in the treatment of MF/SS.

Doxorubicin and pegylated liposomal doxorubicin

Doxorubicin (AAN, hydroxydaunorubicin, or Adriamycin) is currently the most commonly used anthracycline for advanced CTCL. It is used for the treatment of NHL as part of the CHOP regimen. It is also FDA approved for the treatment of HIV-related Kaposi sarcoma. Doxorubicin monotherapy in MF was first reported by Levi and colleagues in 1977.[84] Thirteen patients with MF (described as "advanced disease," including 10 with tumors, 8 with lymph node involvement, and 4 with visceral involvement) were treated with a single IV dose of 60 mg/m^2, repeated in 21-day intervals, and continued for 3 doses beyond maximum clinical response for those who achieved remission. The investigators reported an ORR of 85%, including 23% CR. One patient with preexisting heart disease experienced cardiotoxicity with fatal congestive heart failure. In a dose-escalation study with pegylated liposomal doxorubicin (Doxil or Caelyx), Wollina and colleagues[85] reported 30 patients with stage I–IV MF and 1 patient with SS treated with 20 to 40 mg/m^2 1 to 2 times monthly; 26 of 30 patients with MF and the 1 patient with SS achieved a PR with an ORR of 87%, including 43% CR. Di Lorenzo and colleagues[86] reported on 10 patients with stage IVB MF treated with pegylated liposomal doxorubicin 20 mg/m^2 IV every 4 weeks. Unlike the patients in Wollina and colleagues' study, no subjects were noted to have a CR; 3 patients experienced a PR with an ORR of 30%. The investigators attribute the difference in response between the 2 studies to the fact that those in the latter study were characterized uniformly by advanced-stage disease. In a multicenter phase II trial with pegylated liposomal doxorubicin,[87] 19 patients, including 16 patients with MF/SS and 3 with PTCL, were treated with 20 mg/m^2 every 4 weeks for 2 to 8 treatments. The investigators reported an ORR of 81.2% (13/16) in the MF/SS patients, including a CR in 1 of 4 patients with stage I–IIA MF, 6 of 9 patients with stage IIB–IV MF, and 1 of 3 patients with SS. In another study with 25 patients with stage IIB–IVB MF and SS, subjects were administered pegylated liposomal doxorubicin at 40 mg/m^2 monthly for 8 cycles.[88] There was an ORR of 56%, with 5 patients achieving CR and 9 patients achieving PR. Of patients with SS, 1 had CR and 5 experienced PR. In those patients who responded, a median progression-free survival (PFS) of 5 months was observed. In an EORTC-initiated phase II trial for pegylated liposomal doxorubicin, Dummer and colleagues[89] studied a cohort of 49 patients with stage IIA–IVB MF from 9 centers in 6 countries. The patients were treated with 20 mg/m^2 IV on days 1 and 15 every 28 days (1 cycle) for up to 6 cycles. The ORR was 40.8%, including 3 patients with CR and 17 patients with PR. PFS was approximately 6 months in those who responded. In 2014, Straus and colleagues[90] published results of a phase II trial using doxorubicin hydroxychloride liposome injection in 37 patients with stage IB–IV disease, including 10 patients with SS. Subjects were treated with 20 mg/m^2 IV every 2 weeks for 16 weeks. All patients who did not progress also received bexarotene, 300 mg/m^2 daily, starting at week 16 for an additional 16 weeks; 41% responded with a CR observed in 2 patients (both stage IV) and a PR in 12 patients. The median overall survival duration was 18 months; there were 22 deaths after discontinuation of protocol treatment.

As discussed previously, cardiotoxicity may occur with doxorubicin, the risk of which may be reduced by limiting the cumulative dose to 450 to 550 mg/m^2.[91] Additional side effects include dose-dependent hematologic toxicity (including severe neutropenia), GI symptoms, palmoplantar erythrodysesthesia, and alopecia.

Daunorubicin and liposomal daunorubicin

Similar to doxorubicin, daunorubicin (daunomycin or Cerubidine) is a topoisomerase inhibitor anthracycline.[78] Although there has been more utilization of liposomal doxorubicin in MF/SS, liposomal daunorubicin (DaunoXome) also has shown activity in MF/SS. In a case series of 3 patients with tumor stage MF receiving liposomal daunorubicin, at 20 to 40 mg/m^2 once every 3 to 4 weeks, all 3 patients responded.[92]

Liposomal daunorubicin is FDA approved for the treatment of advanced HIV-associated Kaposi sarcoma. Myelosuppression, infections, alopecia, neuropathy, and cardiotoxicity occur, although grade 3 and 4 reactions are less common.

Epirubicin (Ellence)

The anthracycline, epirubicin (Ellence), is comparable to doxorubicin and has been described in a multiagent regimen similar to CHOP but without vincristine.[93] In the patient reported, however, who had stage IB disease, skin-directed therapies are standard and not multiagent chemotherapy. Several other cases with modified CHOP regimens have also been described replacing epirubicin for doxorubicin.[94,95] It is currently not known if epirubicin has any advantage over doxorubicin in multiagent regimens for MF/SS. Moreover, foregoing vincristine is not known to be significantly safer or superior to standard CHOP.

Idrarubicin

Idrarubicin (4-demethoxydaunorubicin or Idrarubicin) is an anthracycline approved by the FDA for the combination treatment of acute myeloid leukemia in adults. It is currently not known if idrarubicin has any advantage over doxorubicin in the treatment of MF/SS. It has been reported in combination with etoposide, idarubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (VICOP-B) in advanced MF, but there were no responses observed in SS[96] (see **Table 2**).

Etoposide

Etoposide (VP-16, VP-16-213, or epipodophyllotoxin) is a semisynthetic derivative of podophyllotoxin, a plant toxin. It is FDA approved for small cell lung cancer, treatment of testicular tumors, and part of combination chemotherapy regimens for hematologic malignancies. It is available in both oral and IV formulations. Etoposide functions primarily via reversible binding to DNA topoisomerase II, which results in the inability of this enzyme to repair double-stranded DNA breaks and subsequent cell death. Additionally, it induces single-strand and double-stranded DNA breaks.[2]

Etoposide as monotherapy in MF/SS is not well studied and consists predominantly of single case reports. Jacobs and colleagues,[97] in 1975, reported a patient with tumor-stage MF who experienced CR to etoposide, 60 mg/m^2 IV for 5 days, given every 2 weeks. The total duration of treatment was not reported. The investigators also reported a second patient[98] with stage III MF who achieved CR with the same induction regimen for a total of 5 infusions, followed by monthly maintenance courses of 60 mg/m^2 IV and oral etoposide 100 mg/m^2 twice weekly for 3 weeks. Molin and colleagues[99] treated 9 patients with MF/SS (1/9 plaque stage and 8/9 tumor stage) with etoposide, 100 mg IV daily $\times$ 5 days every 2 to 3 weeks induction therapy, followed by 100 mg daily $\times$ 5 days during maintenance. Four of these patients also received concomitant cyclophosphamide. CR occurred in 2 patients and PR in 3; of these, 1 CR and 1 PR were treated with single-agent etoposide. In all responders, disease progression eventually occurred after 4 to 6 months. Nasuhara and colleagues[100] described a patient with MF with pulmonary involvement who experienced CR of over 2 years' duration with oral etoposide, 200 mg weekly, and prednisolone. He had previously been treated with combination chemotherapy with CHOP without any impact on skin lesions. Onozuka and colleagues[101] reported a patient with stage III MF treated with 150 mg IV, 3 times per week for 9 weeks, followed by oral etoposide, 25 mg daily for 21 days every 4 weeks; this therapy was continued for 60 months, 36 of which he experienced CR. Miyoshi and Noda[102] described a patient with SS (criteria not defined) who experienced CR for 4 years with oral etoposide; the dose used was not specified, however. Hirayama and colleagues[103] also reported a patient with SS who experienced CR with etoposide therapy; he was administered 25 mg orally with concomitant MTX of 10 mg weekly, with response maintained for 4 years.

Etoposide is generally well tolerated. Side effects predominantly involve myelosuppression and may be dose limiting. Other adverse effects include GI symptoms (nausea and vomiting), mucositis, and alopecia.[2] Chronic etoposide therapy has also been associated with acute myeloid leukemia. This complication has been reported 15 to 100 months after initiation of therapy, with increased risk associated with total cumulative dose as well as increased treatment frequency (ie, weekly or twice-weekly therapy compared with alternate week therapy).[102,104,105]

INTERLEUKINS

Interleukin-2

Interleukin (IL)-2 (aldesleukin or Proleukin) is a 15-kD polypeptide produced by activated CD4$^+$ lymphocytes. Overall, IL-2 stimulates activation, proliferation, and maintenance of T-helper lymphocytes in vivo and in vitro.[106] Although its antitumor effects are not well understood, they have been observed in various tumors. In MF/SS, IL-2 is thought to prevent and control disease progression through a favorable influence on cytokine milieu, including T-helper cytokine balance in immune responses.[107] IL-2 is FDA approved for the treatment of metastatic renal cell carcinoma and metastatic melanoma.

Nagatani and colleagues[108] first reported the successful treatment of a patient with tumor-stage MF treated first with intralesional IL-2 and then systemic IL-2 monthly. He maintained CR for 13 months. Rybojad and colleagues[109] reported a patient with stage IIB MF with a cytotoxic immunophenotype (CD8$^+$ and CD4$^-$) post–total skin electron beam radiation and autologous bone marrow transplant who underwent induction therapy with IL-2 IV infusion of 10 million units/m^2/d for 5, 4, and 3 consecutive days every 2 weeks followed by 5 monthly maintenance courses of 10 million units/m^2/d for 2 days. The patient achieved a CR and remained without evidence of disease 10 months after discontinuation of therapy. Marolleau and colleagues[110] evaluated 3 patients with MF and 3 with SS treated with IV

IL-2 20 million units/m^2 on days 1 to 5, 14 to 17, and 28 to 30 (induction) followed by 2 days per month for 5 months (consolidation). At the end of consolidation, 2 of 3 patients with MF (stages IIB–IVA) experienced a CR; a PR was seen in 1 of 3 SS patients. In a follow-up letter, it was observed that 2 of the patients with a CR continued to have response at 56 and 63 months post-treatment.[111]

Gisselbrecht and colleagues[112] performed a phase II study with 5 patients with MF (all stage IV) and 2 patients with SS treated with IV infusions of 20 million units/m^2/d for 5, 4, and 3 days on weeks 1, 3, and 5 followed by an optional monthly maintenance therapy of 5 days. One patient had CR and 4 had a PR with an ORR of 71%. The patient with CR had a continued response for 29 months after initial response. In a phase II study using subcutaneous injections, Querfeld and colleagues[107] evaluated 22 patients with MF. Eleven MUs were injected for 4 consecutive days per week $\times$ 6 weeks followed by 2 weeks' observation and repeated for 8 weeks as tolerated. Only 4 patients responded (18%; 1/1 stage IA, 1/6 stage IB, 0/1 stage IIA, 1/3 stage IIB, 1/4 stage III, and 0/7 stage IVA/SS) and no CR was noted. The median event-free survival was 3 months.

Side effects include flulike illness (fever, chills, and fatigue), GI symptoms (nausea and vomiting), weight gain, elevated creatinine, hypotension, cytopenia, vascular leak syndrome, neurologic symptoms, and cardiac toxicity.[2,107,110]

Interleukin-12

IL-12 acts as a potent inducer of IFN-γ by T cells and natural killer cells and directly stimulates cytotoxic T-cell activity.[106,113] In advanced stages of CTCL, peripheral blood dendritic cells (which are producers of IL-12) are depleted in number and function with a concomitant decrease in IL-12 production.[106,114–116] Additionally, diminished IL-12 levels may occur due to increased IL-10 production by malignant T cells.[113] Recombinant human IL-12 has been evaluated in the treatment of MF/SS. Currently, there are no FDA-approved uses for IL-12.

In a phase I dose-escalation trial, 7 patients with MF (2 with T1, 3 with T2, 2 with T3, 2 with T4 skin stages, and 3 with SS) received 50, 100, or 300 ng/kg of IL-12 subcutaneously twice weekly for up to 24 weeks.[117] Each patient with T3 disease received the injections directly into tumor lesions. The ORR was 56% with 2 patients achieving CR (both T2) and 3 with PR (2 with T1 skin stage and 1 SS). In patients with tumors, there was flattening and/or resolution of the tumors treated intralesionally, but new lesions developed at other sites. In a phase II trial, Rook and colleagues[118] evaluated 23 patients with stage IA–IIA MF treated with subcutaneous IL-12 100 ng/kg twice weekly $\times$ 2 weeks with subsequent increase to 300 ng/kg twice weekly for up to 24 weeks.[119] There was an ORR of 43% (10/23), all of which were PRs. Although no CRs were observed, many of those with a PR had extensive clearing of skin lesions.

Adverse effects of IL-12 are generally mild and short lived. These include fatigue, headache, myalgias, injection site reaction, neutropenia, diarrhea, depression, and anxiety.[113,117–119] One death from autoimmune hemolytic anemia has been observed,[119] but it was unclear if this was directly due to IL-12 administration or secondary to an infection.

PURINE NUCLEOSIDE PHOSPHORYLASE INHIBITORS: FORODESINE

Purine nucleoside phosphorylase (PNP) catalyzes phosphorolysis of deoxyguanosine to guanine and ribose 1-phosphate[120,121] Inhibition of PNP in T lymphocytes results in the accumulation of deoxyguanosine triphosphate, which in turn inhibits DNA synthesis with resultant suppression of cell proliferation.[121,122] Selective T-cell depletion occurs with PNP inhibition due to a relatively high level of kinase and low level of nucleotidase activity compared with those in other cells.[123–125] Forodesine (BCX-1777 or immucillin H) is a potent inhibitor of PNP that is available orally and in IV formulation. It has been shown to inhibit the proliferation of T lymphocytes in vivo and in vitro.[121,122,126] Forodesine has been examined in several studies for the treatment of MF/SS.

In a study of 13 patients (described as stage IIB–IV with all but 1 $\geq$ stage III), IV forodesine of 40 to 320 mg/m^2 was administered on day 1 followed by 8 doses every 12 hours (1 cycle) and repeated in 16-day intervals for a total of 3 cycles at 2-week intervals. Nine patients (69%) showed some degree of response.[127] Duvic and colleagues[128] reported a phase I/II trial of 37 patients with stage IB or greater CTCL. Patients were treated with oral forodesine, 40 to 320 mg/m^2 daily for 4 weeks. It was not reported how many of these patients represented MF/SS versus other cutaneous lymphomas. In patients with IIB or greater disease, the ORR was 53.6%, including 1 patient with a CR and 9 with a PR. The median duration of response was 127 days. Dummer and colleagues[129] recently published a phase II multicenter study of forodesine in 144 individuals, in whom 101 patients with stage IIB or greater disease were assessed for efficacy of the drug. Patients were administered 200 mg orally daily

(approximately equivalent to 80 mg/m^2). An ORR of 11% was noted. The lower response rate compared with prior studies was thought possibly due to the lower dose of medication administered in this study.

Forodesine is generally well tolerated. Side effects include nausea, fatigue, reversible lymphopenia, and cutaneous infections.[127,129]

PROTEASOME INHIBITORS: BORTEZOMIB

Bortezomib (Velcade) is a cell-permeable dipeptide boronic acid that reversibly inhibits the β5 subunit of the proteasome. Multiple pro-oncogenic factors are under proteasome control, such as transcription factors, cyclins, cyclin-dependent kinase inhibitors, and apoptotic factors.[130–132] The antitumor acitivity of bortezomib likely varies among tumor types. It is FDA approved for IV treatment of multiple myeloma and mantle cell lymphoma. Only 1 study has evaluated the efficacy of bortezomib in MF. In a phase II trial, Zinzani and colleagues[133] evaluated 10 patients with MF (1 stage IIA, 3 stage IIB, and 6 stage IVA/B) treated with 1.3 mg/m^2 twice weekly for 2 weeks followed by 1-week rest period for up to 6 cycles. A response was noted in 7 patients (70%), including 1 CR and 6 PR. The duration of response was 7 to 14 months; the patient with a CR continued to be in remission 12 months after initial response.

Bortezomib is generally well tolerated; toxicities include neutropenia, thrombocytopenia, and sensory neuropathy. In trials for multiple myeloma, asthenia, GI symptoms, and headache were also documented.[2]

MULTIAGENT CHEMOTHERAPY

Although there are no large controlled studies of multiagent chemotherapy regimens in MF/SS, multiagent chemotherapy is the first-line treatment, along with clinical trials, for most aggressive/rapidly progressive CTCLs (including transformed MF).[134] Although the mainstay is the CHOP regimen,[135] first-line treatment also includes multiagent etoposide, vincristine, doxorubicin, bolus cyclophosphamide, and oral prednisone (EPOCH)[136] and hyper–cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD) alternating with high-dose MTX and cytarabine.[137] For individuals who are candidates for cell transplant, second-line multiagent therapy includes dexamethasone, cisplatin, and cytarabine (DHAP); etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP); gemcitabine, dexamethasone, and cisplatin (GDP); gemcitabine and oxaliplatin (GemOx); ICE; and mesna, ifosfamide, mitoxantrone, and etoposide (MINE).[50,134,138–143] Overall, however, the efficacy of multiagent chemotherapy in the treatment of MF/SS is not well established. Studies that have evaluated various multiagent treatment regimens have often included other concomitant treatments, such as photopheresis or IFN administration, further hindering evaluation of their efficacy. Additionally, despite oft-reported high initial response rates, the duration of response is frequently short lived. Studies that have used multiagent chemotherapy in MF/SS are summarized in **Table 2**.

SUMMARY

Despite recent advances in the development of more targeted therapies in MF/SS, traditional chemotherapies remain an important modality for induction therapy, with some agents used as maintenance therapy. These agents generally target proliferating cells and, therefore, have significant toxicities. Nevertheless, as a category, traditional chemotherapies provide remissions as good as most other therapies and, therefore, must be relied on until more targeted therapies are developed. Other agents, including ILs, phosphorylase inhibitors, and proteasome inhibitors, may have a more significant role in treatment after further study.

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