The use of purine analogues and infections

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In the 1980s, the purine analogues che-
motherapy agents, fludarabine, deoxy-
coformycin, chlorodeoxyadenosine, were
introduced into clinical usage for the care
of patients with a variety of hematologic
malignancies. These drugs have been main-
ly used in indolent lymphoproliferative neo-
plasms with effective hematologic respons-
es, but they have been accompanied by a
different spectrum of infections because of
selective T-cell abnormalities which these
agents determine.

Fludarabine alone

Fludarabine was first introduced in the
armamentarium of the haematologist to
treat resistant CLL. The traditional manage-
ment of patients with CLL needing therapy
was the use of chlorambucil with or without
steroids or successively other alkylating
agent-based regimens. Initially the purine
analogues fludarabine, 2-chloro-deoxy-
adenosine and pentostatin alone or associ-
ated with other antineoplastic drugs were
explored in previously treated patients.
Increasingly purine analogues are being used
more and more as initial therapy for patients
with CLL. Fludarabine is very active against
indolent lymphoid neoplasms; its efficacy is
due to its ability to reduce the number of
lymphoid cells rapidly, originating also some
cases of tumor lysis syndrome. Profound and
prolonged suppression of the CD4 count
occurs, with median CD4 counts decreasing
<200/mL in 2-3 months of therapy.

Although the CD4 count improves in the
first 3 months from the end of treatment,
quantitative abnormalities may persist for
1-2 years. This immunosuppression and neu-
tropenia secondary to therapy determined
an increased number of infections, particu-
larly by opportunistics, also in the absence of
neutropenia or steroid therapy.

In the first review of the literature[1] relat-
ed to fludarabine-associated opportunistic
infections which evaluate 2,269 patients
with low-grade malignancies who received
fludarabine therapy, the most notable infec-
tious complications were respiratory tract

infections and unexplained fever; 3.2% of
these patients developed opportunistic infec-
tions during or after fludarabine treatment;
97% of these infections occurred in patients
who were previously treated with alkylator
agents or corticosteroids. Opportunistic
infections were due to *Pneumocystis carinii*
(33%), mycoses (30%), *Listeria monocyto-
genes* (14%), also after many months from
completion of therapy, *mycobacteria* (9%),
CMV (7%), *Herpes* (6%); a very high inci-
dence of localized *Varicella zoster* was also
noted in several studies, particularly in
patients with a CD4 count >50 cells/mL.[2]

The majority of these infections don't
appear to be related to neutropenia or low
levels of immunoglobulins. The high inci-
dence of opportunistic infection in patients
previously treated with alkylator agents or
steroids reported by some authors[1, 3-4] sug-
gests that the utilization of steroids before
and after fludarabine treatment increases
immunosuppression; it also determines
more opportunistic infections which seem
to be less frequent in other salvage chemo-
therapy cycles containing steroids, in which
only 1.5% of patients had opportunistic
infections.[5-7] Finally, the risk of infections
during fludarabine therapy increases with
the use of higher doses than recommended,
or when different purine analogues are
associated or sequentially performed.[8,9]
More recently, the comparative assessment
of first–line randomized therapy with flu-
darabine and two anthracycline-containing
regimens in 938 untreated patients was
performed by the French Cooperative
Group[10]; incidence of infections were simi-
lar in the three randomized groups, where-
as fludarabine induced, compared to other
two regimens, more frequent myelosup-
pression; however, infection rate was 5%
and opportunistic infections were absent.
This could be related to the fact that flu-
darabine was administered to untreated
patients.

Long-term follow-up of 174 patients
receiving fludarabine regimens as initial
therapy with or without steroids was recent-

ly published by M.D. Anderson Cancer Center;[11] depression of CD4 and CD8 counts was marked in this study, occurring mainly during the first 3 courses of therapy, as reported in other studies.[12,13] No difference in these values was noted between patients treated with or without prednisone; recovery from this effect, after fludarabine was discontinued, was slow. Despite the persistent T-cell suppression, infections and febrile episodes were uncommon during hematologic remission and decreased with time to follow-up. No association was noted between infection rate and CD4 level at the end of fludarabine treatment. Of the 137 patients who achieved response, 94 infectious episodes occurred during remission, above all dermatomal *Herpes zoster*, (19 cases); *Herpes simplex* reactivation (5 cases). One episode of septicaemia by *Listeria monocytogenes* and one CMV infection were seen. There was a strong association with the quality of the remission and the probability of patients developing these episodes; in addition, infection or febrile episodes decreased as length of remission increased.

Otherwise, opportunistic infections have been frequently associated with fludarabine treatment in case of patients having received previous chemotherapy. In fact the association of fludarabine and prednisone studied by O'Brien and coworkers in 160 pretreated and 95 untreated patients[10] showed that the incidence of sepsis and/or pneumonia was significantly correlated with the extent of prior therapy and with Rai stage, and ranged from 3% of courses in the previously untreated Rai 0-II stage patients, to 13% of courses in the previously treated Rai III-IV stage patients. The incidence of minor infections instead was 12% and did not vary in different patient subgroups. Several episodes of atypical infections were noted in patients treated with fludarabine and prednisone; 13 patients developed either *Listeria* sepsis or *Pneumocystis carinii* pneumonia and all were heavily pretreated and had more advanced stage disease. The importance of previous chemotherapy courses was underlined in the comunications about severe infectious toxicity found in the first studies with fludarabine as salvage therapy in 402 CLL patients with CLL who received fludarabine with or without prednisone.[2] In this population unexpected opportunistic infections as *Listeria monocytogenes* and *Pneumocystis carinii* were diagnosed in 7% of pretreated patients who recived fludarabine plus prednisone and in 1% of previously untreated patients who received the combination (*p=0.003*). The development of refractoriness to fludarabine is associated with significant likelihood of infections. Keating *et al.*[14] reviewed the response to salvage therapy in patients refractory to fludarabine; the major cause of morbidity and deaths was infections, above all bacterial, but opportunistic infections such as fungi, *P carinii, acid-fast bacilli* and *Legionella* were also prominent. The high percent-

age of infections was confirmed by Perkins et al.[15] in which 24/27 (89%) patients with fludarabine refractory CLL developed serious infections. Now, risk factors for infections during single-agent fludarabine therapy are well characterized and include concurrent corticosteroid use, pretreated disease, advanced disease stage, failure to achieve RC, fludarabine-refractory disease, high serum $\beta2$-microglobulin level, impaired renal function, and baseline neutropenia[12,13]

Infections in fludarabine-combined regimens

Fludarabine is the most effective single agent in the treatment of indolent lymphoid malignancies, but complete disease remissions remain uncommon with single-agent fludarabine and overall survival is not superior to traditional alkylator based therapy, providing the rationale for the development of fludarabine based combination regimens. These regimens have been reported to achieve a high response rate in both CLL and indolent lymphomas, but severe infections occur in up to one-third of patients. However, data on infections during fludarabine-based combination chemotherapy are sparse, and may not be comparable to the data on single-agent fludarabine therapy.

O'Brien *et al.* showed that the association of fludarabine ad cyclophosphamide at different dosages in CLL untreated and pretreated patients seems to have a significant advantage compared to fludarabine alone.[16] Pneumonia or sepsis occurred in 25% of patients and fever of unknown origin, frequently associated with neutropenia, occurred in another 25% of patients. Since myelosuppression and/or infection resulted in subsequent dose reductions, when infections are shown as percentage of total courses given, they were observed in 10% of all cycles of chemotherapy. Some atypical infections (5.4%) and reactivation of *Herpes simplex* (8%) and *zoster* (5%) were noted. Finally, more frequent sepsis or pneumonia were observed in patients refractory to fludarabine at the start of combination chemotherapy (48% vs 18%, *p<0.001*). A lower dose of cyclophosphamide seems to have the same efficacy with less severe infections.[17] Flinn *et al*[18] reported in previously untreated indolent lymphoid neoplasms that the same chemotherapy regimen determined 11.7% of infections, with reactivation of *Herpes zoster* and *chronic hepatitis B*, and *Pneumocystis carinii* pneumonia in a patient who had stopped his cotrimoxazole prophylaxis. As front-line chemotherapy in patients with indolent or mantle-cell lymphoma, the association of fludarabine and idarubicin or mitoxantrone seems to have little infectious toxicity.[19,20]

An attempt to develop a predictive model for infection[21] during fludarabine-based regimens has been recently published. Six risk factors were associated with infectious complications in patients treated with flu-

darabine–based combination regimens: age > 60 years, at least 3 previous therapies, previous fludarabine exposure, time from diagnosis to current treatment > 3 years, performance status > 2 and baseline neutrophils <2.0 x 10⁹/L. Compared with patients with 0-2 risk factors, patients with at least 3 risk factors had higher infection rate (26% vs 7% per cycle, $p<0.0001$), more grade 4 neutropenia (41% vs 8% per cycle, $p<.0001$), and more neutropenic sepsis (\5% vs 1% per cycle, $p<0.0001$). Moreover there was a significant correlation between risk of infection and quality of disease response to therapy: 5% of infections for complete responders, 15% for partial responders and 35% for nonresponders ($p<0.0003$).

Other purine analogues

The rate of infections was similar in CLL patients treated with CdA. Robak et al (22) administered 2-CdA to 113 patients with CLL > 55 years. Infections or FUO occurred in 26% of patients. Neste et al.[23] compared the incidence of infections in the 6 months preceding treatment with 2-CdA with the 6 months following therapy in 95 patients and showed a doubling of infection rate after treatment with CdA. Also the association of 2-CdA and cyclophosphamide in lymphoproliferative neoplasms[24] showed that WHO grade 3-4 infections occurred in 42% of patients. A similarly increased incidence of infections was noted with the use of pentostatin[25] in pretreated patients. Infections are a dangerous complication also following pentostatin treatment, which is mainly used in hairy cell leukaemia. In this disease bone marrow cellularity may severely decline to< 25% after pentostatin and tends to remain stable thereafter. For these reasons the risk of infections is particularly high and imposes cautious use of this drug. Instead in the long term follow-up of 365 patients (179 untreated) with hairy cell leukaemia after cladribrine treatment[26] opportunistic infections were rare (7 *Herpes zoster*, 2 *hepatitis* C, 2 *mycobacteria*) and only 3 deaths due to infection were seen. Similar results were seen at long-term follow-up in hairy cell leukaemia patients treated with pentostatin.[27]

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