The use of purine analogues and infections

In the 1980s, the purine analogues chemotherapy agents, fludarabine, deoxycoformycin, chlorodeoxyadenosine, were introduced into clinical usage for the care of patients with a variety of hematologic malignancies. These drugs have been mainly used in indolent lymphoproliferative neoplasms with effective hematologic responses, 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 management 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-deoxyadenosine and pentostatin alone or associated 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 neutropenia secondary to therapy determined an increased number of infections, particularly by opportunistics, also in the absence of neutropenia or steroid therapy.

In the first review of the literature related to fludarabine-associated opportunistic infections which evaluate 2,269 patients with low-grade malignancies who received fludarabine therapy, the most notable infectious complications were respiratory tract infections and unexplained fever; 3.2% of these patients developed opportunistic infections 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 monocytogenes (14%), also after many months from completion of therapy, mycobacteria (9%), CMV (7%), Herpes (6%); a very high incidence of localized Varicella zoster was also noted in several studies, particularly in patients with a CD4 count >50 cells/mL.

The majority of these infections don’t appear to be related to neutropenia or low levels of immunoglobulins. The high incidence of opportunistic infection in patients previously treated with alkylator agents or steroids reported by some authors suggests 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 chemotherapy cycles containing steroids, in which only 1.5% of patients had opportunistic infections. 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.

More recently, the comparative assessment of first–line randomized therapy with fludarabine and two anthracycline-containing regimens in 938 untreated patients was performed by the French Cooperative Group; incidence of infections were similar in the three randomized groups, whereas fludarabine induced, compared to other two regimens, more frequent myelosuppression; however, infection rate was 5% and opportunistic infections were absent. This could be related to the fact that fludarabine 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; 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. 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 sepsicaemia and 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 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 communications 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. In this population unexpected opportunistic infections as Listeria monocytogenes and Pneumocystis carinii were diagnosed in 7% of pretreated patients who received 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. 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 percentage of infections was confirmed by Perkins et al. 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 β2-microglobulin level, impaired renal function, and baseline neutropenia.

**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 and cyclophosphamide at different dosages in CLL untreated and pretreated patients seems to have a significant advantage compared to fludarabine alone. 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. Flinn et al. 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.

An attempt to develop a predictive model for infection 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 10^9/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<0.0001), and more neutropenic sepsis (15% 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 cladribine 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).

References


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