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## Management of complications: infections, autoimmunity, cytopenias

### Infections

In untreated patients or in patients treated with alkylating agents, most infections are bacterial (*Haemophilus influenzae*, *Klebsiella pneumoniae* *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Escherichia coli*). Respiratory tract is the most frequent site of infection. Fungal and viral infections are rare and generally occur in heavily pre-treated patients; hypogammaglobulinemia and treatment-related neutropenia play a major role.

The pathogenesis of infections related to purine analogues is multifactorial: qualitative and quantitative T-cell abnormalities, with a decrease in CD4 cells, persisting for months after treatment are most important. The infections may be bacterial, fungal (*Candida*, *Aspergillus*), viral [cytomegalovirus (CMV), hepatitis, reactivations]. Patients treated with alemtuzumab present prolonged and profound lymphocytopenia. They are at risk for opportunistic infections beginning 3 to 4 weeks after the start of therapy (which corresponds to the nadir CD4 and CD8 counts) and lasting at least 12 to 16 weeks following completion of therapy. The spectrum of infections includes bacterial septicaemias and pneumonias, as well as opportunistic infections with

CMV, *Aspergillus*, and *Pneumocystis jirovecii* pneumonia (PcP).<sup>1</sup> Rituximab has been recently used in association with fludarabine and cyclophosphamide<sup>2</sup>: 16% of treated patients suffered major infections (sepsis, pneumonia, or infection requiring hospitalization).

### Drug prophylaxis

The decision to perform an antibiotic prophylaxis must be taken by carefully considering risk factors, recent and past therapies and CLL history; no data are available from randomized trials and the approach must often be decided in every single patient and every single situation.

Risk factors include: the degree of hypogammaglobulinemia, advanced and/or progressive disease, the coexistence of neutropenia, the association of steroids, previous infectious episodes, increased creatininemia after purine analogues, lower CD4<sup>+</sup> counts for herpes infections.

Alkylating agents: drug prophylaxis is probably effective only in selected high risk patients.

### Purine analogues

Prophylaxis for PcP has been recommended for all patients receiving purine analogues;<sup>3</sup> however, in patients treated with fludarabine as first line therapy the incidence of opportunistic infections is low even when no prophylaxis

laxis was used. PcP infections were seen in less than 1%<sup>4</sup> and were not seen in another large series of patients,<sup>5</sup> neither treated with fludarabine and cyclophosphamide nor in those treated with fludarabine only: for this reason these authors do not recommend prophylaxis in untreated patients. When prophylaxis is initiated, it should be continued for at least 2 months after the end of therapy.

Viral infections are common; varicella zoster virus (VZV) infection and post-herpetic neuralgia appear particularly frequent.<sup>6</sup> Prophylaxis is recommended in patients with risk factors or with previous history of HV infections. It must be continued for at least 3–4 months after the end of therapy.

Alemtuzumab: when heavily pre-treated patients with advanced disease receive alemtuzumab, the incidence of opportunistic infections is very high; up to 60% of patients suffer CMV reactivation. Even in patients receiving prophylaxis with famcyclovir, CMV viremia was positive in 15% of patients.<sup>7</sup> In untreated patients the risk of opportunistic bacterial and fungal infection is lower. With correct prophylaxis, the incidence of PcP is reduced. Prophylaxis against PcP and herpes virus is recommended for all patients. They must be continued up to 6 months after the completion of therapy.<sup>8</sup> Antifungal primary prophylaxis is generally recommended only in selected patients. A significant rate (20–25%) of patients treated with alemtuzumab may suffer grade 4 neutropenia in every disease phase;<sup>9,10,11</sup> it usually develops early, during the first weeks of therapy and generally reaches a nadir after 4 or 6 weeks. Grade 3 and 4 thrombocytopenia and neutropenia occurred in 30% and 26% of patients with relapsed or refractory CLL treated with fludarabine and alemtuzumab. It resolves in many cases after stopping therapy: otherwise G-CSF may be used and it is generally effective. G-CSF is suggested when neutropenia recurs after resuming therapy.

According to Osterborg,<sup>12</sup> therapy must be suspended when ANC is lower than 250 or in case of symptomatic thrombocytopenia.

CMV reactivations are common even after first-line therapy. Surveillance of CMV infection to detect initial reactivation, using PCR or pp65 antigenemia has been proposed;<sup>13</sup> it permits an early pre-emptive therapy. However, PCR or pp65 antigenemia must be performed in all patients with fever of unknown origin or a clinical picture suspected for CMV infection. If such tests are not available, an anti CMV therapy must be considered in these patients. Pre-emptive therapy can be performed with gancyclovir or foscarnet.

For PcP prophylaxis Trimethoprim-sulphamethoxazole, double strength (BD twice weekly). As alternatives: oral dapsone, nebulised pentamidine or oral atovaquone. It must be administered for a minimum of 6 months after fludarabine or until CD4 counts has recovered.

Prophylaxis for *Herpes virus* can be performed with Famcyclovir (500 mg BD) or valacyclovir (500 mg daily or BD) or acyclovir (200 mg TDS).

### **Hepatitis**

HBV reactivations and infections have been described in CLL patients after therapy with Rituximab, which depletes B-cells<sup>14</sup> and alemtuzumab.<sup>15</sup> Risk patients are hepatitis B surface antigen (HbsAg)-positive patients and also those with viral persistence after natural infection, with a positive hepatitis B core antibody (HBcAb) and negative HbsAg. In all patients a screening of HBV and HCV markers must be performed. The clinical picture of HBV reactivation ranges from transitory alterations of liver function tests in asymptomatic patients to fatal hepatitis. Lamivudine was shown to reduce reactivation after chemotherapy from 24–53% to 0–5%.<sup>16</sup> Prophylaxis with lamivudine is mandatory for HbsAg positive patients;

in patients positive for hepatitis B core antibody (HBcAb) and negative for HbsAg both prophylactic lamivudine and close monitoring with lamivudine administered at the first alterations of liver function tests have been proposed.<sup>16</sup> It should be initiated some weeks before chemo-immunotherapy at a dosage 100 mg/d and continued for at least 6 months after its completion. A case of B hepatitis has developed two months after the end of lamivudine;<sup>15</sup> however the same drug was effective for treatment. The rate of mutations carrying to lamivudine-resistance is proportional to the duration of therapy; it was reported a 24% rate after 1 year of therapy. Adefovir and entecavir must be considered in these patients.<sup>17</sup>

Less data are available for HCV. Treatment with ribavirin and pegylated interferon has been recently reported in BMT patients with chronic HCV; response rate in immunocompromised patients is generally low.

#### **Immunoglobulin replacement**

Reduction of serum immunoglobulins level relates with the risk of bacterial infections in CLL patients. Some trials have shown that immunoglobulins replacement can actually reduce the rate of bacterial infections in high risk (i.e. with severe hypogammaglobulinemia and/or recurrent bacterial infections) patients.<sup>18-21</sup> However, many reasons limit their use: immunoglobulins are very expensive and their availability is scarce, they have no effects on infections other than bacterial; since the introduction of purine analogues, T-cell defects have become progressively more important in the pathogenesis of infections in CLL patients. Furthermore, no trial has shown that their use is more effective than antibacterial drug prophylaxis, less expensive. According to British guidelines,<sup>3</sup> prophylactic IVIG must be reserved to “patients with hypogammaglobulinemia and recurrent bacterial infections, especially those in whom pro-

phylactic antibiotics have proved ineffective (grade A recommendation, level Ib evidence)”.

#### **Granulocyte colony-stimulating factor**

As no randomized trials has evaluated the use of G-CSF in CLL, no specific guidelines have been developed and their use must be decided as in other cancer patients.<sup>22</sup> It must be remembered that in CLL patients the effect of neutropenia may be higher because it often adds to other risk factors, such in patients treated with purine analogues and/or monoclonal antibodies.

When an infection develops, the principles of treatment are the same as in other immunocompromised patients. Patients and their relatives must know that infections can be severe and sometimes rapidly evolving and that therapy must begin as early as possible. Patients must be evaluated at the first sign of infection, to decide if they can be treated as outpatient or if a parenteral broad spectrum antibiotic must be administered in Hospital.

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#### **Immune cytopenias**

Even if many immunologic mediated diseases have been described in CLL, cytopenias due to antibodies directed to blood cells are prevalent: auto-immune haemolytic anaemia (AIHA), pure red cell aplasia (PRCA), immune-thrombocytopenic purpura (ITP), immune neutropenia.

#### **Auto-immune haemolytic anaemia**

Even if highly different rates have been reported (from <5% to 38%<sup>23-26</sup>), AIHA occurs much more frequently in patients with CLL than in normal people and it represents the most frequent immune complication in these patients.

Reported incidence of AIHA after purine analogues therapy ranges from 2% in untreated

patients to 20% in patients with advanced disease. A statistically significant increase of AIHA after purine analogues than after alkylating agents was shown in a meta-analysis.<sup>27</sup> However most randomized trials in untreated patients did not show a statistically significant increase: a recent randomized trial for untreated patients (CLL4 trial<sup>28</sup> has shown that there were more hemolytic anemias after chlorambucil (13%) than after Fludarabine (10%) or Fludarabine plus cyclophosphamide (4%). The risk of autoimmune complications after a combination of a purine analogue and cyclophosphamide and/or rituximab may be lower than after a purine analogue alone.

Diagnosis, based on direct antiglobulin test (DAT), reticulocytosis, LDH, haptoglobin, urinary urobilinogen, may be more confusing, when compared with idiopathic AIHA: this is due to the fact that false positivity or negativity of the most common diagnostic tests may be induced by CLL itself.

DAT is negative in a significant proportion of patients; the rate of negativity may be higher in patients receiving Rituximab;<sup>29</sup> reticulocytosis may be reduced or absent when bone marrow is largely infiltrated by CLL cells. Elevated LDH may be influenced by CLL itself.

These diagnostic difficulties may partly explain the different incidences reported in literature.

AIHA may occur in different moments of CLL course and this influences prognosis and therapy of AIHA and CLL. It can antedate CLL even of many years,<sup>26</sup> it can present at first diagnosis or at relapse, during remission or during therapy. Even if the same drugs are used, treating AIHA in these different settings may involve different strategies, especially regarding the therapy of CLL. In fact, chemo and/or immunotherapy may have a double role on AIHA: they can induce autoimmunity through their immunosuppressive action or control it reducing the activity of CLL cells implicated in

autoantibody production. When AIHA occurs in progressive CLL, while the patient is not receiving therapy, a correct treatment of CLL may have a major effect also on the immune complication. When AIHA occurs in a patient receiving therapy, the immune complication must be controlled at first, but therapy of CLL must often be resumed in a short time, generally when the patient is still receiving therapy for AIHA. When chemotherapy is resumed the risk of relapse of AIHA is considerable; most patients who have developed AIHA during fludarabine therapy have had recurrent haemolysis on re-exposure to fludarabine.<sup>30,31</sup> The risk of relapse is elevated even if a different therapy is begun.<sup>32</sup> Some patients who will be successfully retreated with fludarabine, while receiving cyclosporine, have been described.<sup>33</sup> Infectious complications are a major risk in patients receiving simultaneously chemo-immunotherapy for CLL and steroids or cyclosporine for an autoimmune complication.

### **Drugs**

**Steroids:** they usually represent first line treatment; initial dosage is 1 mg/kg/day; when a response is achieved, it is progressively reduced. Most patients respond. The risk of opportunistic infection is elevated: an anti-infective prophylaxis must be considered, especially when patients are receiving cytotoxic therapy and in cases of advanced disease.

**Cyclosporine:** it is generally used as second line therapy. A response rate of 62% in AIHA was reported.<sup>33</sup> The median time to best response was 10.5 weeks with a range between 1 and 48 weeks. The median time to initial response was 3 weeks (range, 1 to 13 weeks). The median duration of response was 10 months (range, 1 to 39 months).

### **Intravenous immunoglobulins**

They may be used at a dosage of 400 mg/kg/day for 5 consecutive days; 40% of

responses have been described in patients with AIHA and CLL.<sup>24</sup> Their effect is immediate but transient and they must be used when a rapid increase in Hb is necessary.

### **Rituximab**

Rituximab has been used in many autoimmune complications in CLL patients. Recent case reports suggest that Rituximab can be effective in patients with warm and cold antibody AIHA, ITP and PRCA refractory to other treatments.<sup>3,34-37</sup> Response to Rituximab has been reported in patients with fludarabine-related AIHA<sup>38-44</sup> Different dose regimens have been used, from the *usual* schedule of 375 mg/sqm once a week for four weeks to the same dose infused three or four times a week. Its cost is elevated and it's generally used when other therapies have failed.

### **Splenectomy**

Splenectomy may represent a life saving procedure in patients with cytopenias refractory to other therapies.<sup>45</sup> Some studies have been reported including CLL patients, both with autoimmune complications and with hypersplenism in refractory disease; the operative mortality ranged from 1.5–9% with a morbidity (particularly infections) of 26–54%; laparoscopic splenectomy may reduce treatment related complications. In these patients, generally with advanced CLL, vaccination against meningococcus, pneumococcus and *Haemophilus influenzae* may have low efficacy and long-term antibacterial prophylaxis must be considered.

### **Alemtuzumab**

Karlson<sup>46</sup> reported 5 patients with advanced B-CLL and severe transfusion-dependent AIHA effectively treated with alemtuzumab.

### **Red cell transfusions**

Even if transfused red cells can be destroyed

by autoantibodies, the support with red cells transfusion can be important especially in patients with high grade haemolysis of recent onset, before other therapies can achieve their effect.<sup>47</sup>

### **How to treat CLL in DAT positive patients**

DAT should be performed in all patients at the diagnosis of CLL. When this group of patients must receive treatment, there are no evidences that purine analogues containing regimens may induce higher rates of overt AIHA. In a recent trial by,<sup>28</sup> 64 DAT positive patients entered the trial and were randomized to receive chlorambucil or fludarabine plus cyclophosphamide: overall 18/64 (28%) developed AIHA (versus 7% of DAT negative patients); however the risk of developing overt AIHA was lower (5.8%) in the fludarabine plus cyclophosphamide arm than in chlorambucil arm (39%).

### **How to treat CLL in patients with overt AIHA**

Due to its efficacy as therapy of established AIHA, Rituximab-containing regimens may be attractive for treating these patients. R-CHOP is suggested by some Authors as therapy of choice in these patients.<sup>47</sup> In a series of untreated patients receiving FCR,<sup>29</sup> eight patients had AIHA before treatment; two had resolution of AIHA with FCR alone; three responded to different therapy; one patient had worsening of AIHA with administration of FCR and responded to steroids after discontinuation of FCR. The Authors conclude that the presence of AIHA, at least in untreated patient, should not preclude the use of FCR therapy.

### **Autoimmune thrombocytopenia**

Differential diagnosis of autoimmune thrombocytopenia versus thrombocytopenia due to marrow infiltration may be difficult. No reliable tests are available in clinical setting for anti platelets antibodies. Increase in bone mar-

row megakariocytes is the more reliable diagnostic marker. Due to these reasons, the real incidence is difficult to evaluate. A significant number of cases are associated with AIHA (Evans syndrome). Therapy is based on the same drugs as AIHA. A response rate of 63% after cyclosporine in ITP was reported.<sup>33</sup> Splenectomy may be more effective than for AIHA and it may be used earlier in refractory autoimmune thrombocytopenia. Vincristine has been used.<sup>48</sup> Different reports have shown Rituximab to be effective.

#### **Antibody-mediated neutropenia**

Antibody-mediated neutropenia is even more difficult to identify than autoimmune thrombocytopenia; it may be confused with neutropenia due to marrow infiltration, chemotherapy or monoclonal antibodies. Three cases of antibody proven autoimmune neutropenia following treatment for CLL (FC, FCR, chlorambucil) have been recently described; filgrastim was successfully used in two cases.<sup>49</sup>

#### **PRCA**

PRCA is an infrequent complication in CLL with reported incidence lower than 1%. It is characterized by an absence of reticulocytes in the peripheral blood, while platelet and neutrophil counts are normal. Red blood cell precursors in the bone marrow examination are markedly decreased or absent while myeloid and megakaryocytic lines are normal. The therapy is based on the same drugs used for

AHIA. Recently effective treatment with Rituximab and Campath were reported.<sup>33,50</sup>

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### **Non-autoimmune cytopenias**

#### **Anaemia**

Anaemia in untreated patients in related to advanced stage of disease. It may be caused by chemotherapy: among these patients, some trials have shown that erythropoietin can reduce transfusion requirement and improve quality of life. Inclusion criteria were not homogeneous in these trials: however patients with relative erythropoietin deficiency should have better response.<sup>22</sup>

#### **Neutropenia**

The most frequent cause of neutropenia is chemotherapy. Prophylaxis of infections is discussed earlier in this article. Less frequent causes are autoimmunity, Rituximab, hypersplenism.

#### **Thrombocytopenia**

When not due to autoantibodies, thrombocytopenia may be related to advanced disease, chemotherapy, hypersplenism.

#### **Splenectomy**

It has been used for refractory cytopenias, especially in patients with massive splenomegaly refractory to chemotherapy. It is effective on anaemia and thrombocytopenia in many cases.<sup>22</sup>

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