chapter 5

General principles of treatment

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introduction

Treatment decisions depend not only on several factors, which may be summarized as follows: impact of disease, efficacy of the therapy and potential side-effects, but also on whether the disease has metastasized or not. As discussed in the previous chapters, hematological malignancies are generally systemic at diagnosis. It is more the exception than the rule that we are faced with local disease which may be treated with local therapies such as surgery or radiotherapy. Radiotherapy, however, has, historically, an important role especially in the treatment of Hodgkin’s disease. Since the introduction of this treatment modality, subsets of patients with Hodgkin’s disease could be cured. Currently, however, we are increasingly aware of potential long-term side-effects of our potent treatment options which result in new and adjusted recommendations especially in curable diseases where long-term side-effects have a significant impact.

In the treatment of hematological malignancies, several treatment approaches can be discriminated as follows: induction, consolidation and maintenance therapy. Stem-cell transplantation (either autologous or allogeneic) is frequently applied. In addition, patients can be treated apart from chemotherapy with monoclonal antibodies (mAb) or radiotherapy. For several diseases wait-and-see policies are also applied.

Induction chemotherapy is a part of an intensive treatment of acute leukemias. The aim is to bring patients in complete remission with one intensive cycle (sometimes two). If patients are in remission, the subsequent goal of the therapy is to prevent relapse. For this aim, consolidation therapy is used. Especially in acute lymphoblastic leukemia (ALL), many treatment protocols also contain maintenance chemotherapy. Generally, this is less immunosuppressive treatment given over a prolonged period of time.

It is increasingly known that there is a significant dose–response relationship in the treatment of many hematological malignancies. One of the first significant side-effects, however, is related to bone marrow depression. To make high-dose therapy possible and to prevent long-term bone marrow depression, autologous stem cells can be reinfused after the high-dose therapy. This procedure is called autologous transplantation. Stem cells to be reinfused can be either harvested from the bone marrow or from peripheral blood after mobilization with chemotherapy plus growth factor support.

An alternative approach is the transplantation using the stem cells of a donor [preferably human leukocyte antigen (HLA) identical]. The advantage of allogeneic transplantation is not only the use of noncontaminated stem cells but also especially the transplantation of the immune system of the donor which hopefully results in an immunological graft versus tumor effect (GvT). For this procedure to be effective, one needs effective immunosuppression which was in the past obtained by using the high-dose therapy as also used in autologous transplantation. Increasingly high-dose therapy is replaced by immune-suppressive treatment which enables the graft to grow and to exploit the GvT.

Increasing knowledge has resulted in the discrimination of antigen (Ag) presence on tumor cells. The development of antibodies (Ab) that are directed against these Ags may have a significant antitumor effect. In hematology, the most important mAb is anti-CD20 which is very effective in the treatment of patients with all types of B-cell non-Hodgkin’s lymphoma (NHL). The working mechanisms are not completely elucidated but depend, among others, on complement activation and also antibody-dependent toxicity. Increasingly, mAbs are used in combination with standard chemotherapy, resulting in a higher efficacy.

Historically, radiotherapy is a very effective option in the treatment of hematological malignancies. Relapses in irradiated areas are very rare. The major drawback of radiotherapy, however, is that it is only local therapy and, therefore, not effective against nonvisible areas of malignant diseases and, of course, in not irradiated areas. In the treatment of Hodgkin’s disease, it is now clear that the combination of radiotherapy with some cytotoxic regimens results in an increased likelihood of secondary malignancies which now has resulted in a more limited application of radiotherapy.

In some hematological malignancies where the disease is relatively asymptomatic and cure cannot be achieved with current standard treatments, a wait-and-see policy (sometimes also called watchful waiting) can be applied. Diseases in which wait-and-see policies are applied include early stages of good-risk chronic lymphocytic leukemia, asymptomatic stages of multiple myeloma and myelodysplastic syndromes (MDS) and asymptomatic patients with low-grade NHL.

acute leukemias

In the last decades we have learned that acute leukemias are very sensitive to chemotherapy. We, however, do know that for these treatments to result in survival improvements, they should be very intense and, therefore, result in pancytopenias.
for several weeks. Not only this awareness but also especially the improved supportive care to have patients surviving the prolonged pancytopenias has made a significant contribution to the survival improvement for patients with acute leukemias. Although the results have improved in the last decades, they are still not good enough to consider any treatment as standard treatment. Thus, it is of most importance that patients with acute leukemias are included in well-designed clinical trials.

Currently, standard treatment of patients with acute myelogenous leukemia (AML) consists of induction chemotherapy with combinations of anthracyclins + cytarabine. This combination can result in complete response rates of ~70%–80%. In elderly patients the complete response rate may be less because of the presence of resistance mechanisms in the leukemic cells (e.g., P-glycoprotein). Especially in the elderly, it is clear that treatment should consist of either appropriate induction chemotherapy or only supportive care. Oral chemotherapy (e.g., Hydrea) has no proven advantage over any therapy.

Patients with acute leukemia who have entered a complete remission have a likelihood of >50% to relapse. To decrease this, chance consolidation therapy is necessary. In many protocols, these consolidation courses consist of combinations of anthracyclins, cytarabine or etoposide. Subsequently, autologous stem-cell transplantion or allogeneic stem-cell transplantion (ASCT) should be considered. Because of its toxicity, increasingly, allogeneic transplantion is limited to patients with poor-risk acute leukemia, which can be assessed on the presence of cytogenetic abnormalities at diagnosis.

Patients with promyelocytic leukemia (AML-3) do respond very well on the combination of chemotherapy plus ATRA (all-trans-retinoic acid). These patients may present with clotting and hemorrhagic problems at diagnosis which do respond very well to this treatment. For further details, we refer you to the chapter on Emergencies.

The treatment of patients with ALL should also be according to the strict guidelines. In these patients, in addition to the anthracyclins and cytarabine, drugs such as vincristine, asparaginase, but especially, prednisone have been very important. As in myeloid leukemias, in patients with ALL, complete response rates of 70%–80% can be achieved.

Patients with ALL who have entered a complete remission need consolidation therapy to prevent a relapse. In many protocols, these consolidation courses consist of combinations of anthracyclins, cytarabine or etoposide followed by maintenance therapy. Subsequently, autologous stem-cell transplantion or ASCT may be considered. As in AML, allogeneic transplantion is limited to patients with poor-risk acute leukemia; which can be assessed on the presence of cytogenetic abnormalities at diagnosis.

A small subset of patients with ALL have a t(9;22). It is now increasingly recognized that these patients may benefit from the addition of imatinib to the standard induction chemotherapy. Also, for these poor-risk patients (if possible), ASCT should be considered.

Supportive care consisting of prophylactic antibiotics and prophylactic red blood cell and platelet transfusions have made it possible for the patients to survive the chemotherapy-induced aplastic phase of about 3–4 weeks. Prophylactic antibiotics consisting of a chinolon (e.g. ciprofloxfine) and an antifungal (e.g. fluconazol) are frequently applied.

**myelodysplastic syndromes**

MDS are generally diagnosed in elderly patients. Because of the increased likelihood of comorbidity of these patients, generally the choice is made for supportive care. This can consist of transfusions to correct red blood cell or platelet deficiencies. In addition, especially when infections are the most dominant symptom, prophylactic antibiotics is increasingly gaining acceptance. Some patients with severe anemia and relatively low erythropoietin levels may benefit from erythropoietin therapy.

Younger patients with MDS can be candidates for leukaemia-type induction chemotherapy. Generally, the choice of this treatment is based on prognostic factors and should be part of well-designed clinical trials. After induction and consolidation, autologous stem-cell transplantion and ASCT may be of benefit.

**chronic lymphocytic leukemia**

Patients with chronic lymphocytic leukemia are generally characterized by a long period where no treatment is necessary. Generally, treatment is indicated when the disease results in pancytopenias as a result of bone marrow infiltration with malignant cells. Alkylator therapy (chlorambucil or CVP) may be effective. Invariably, patients will relapse. Reinitiating the same treatment may be effective, however, also other treatment modalities such as the use of fludarabine can also result in high response rates. Alemtuzumab (anti-CD52) is also an effective treatment modality. Also, rituximab may be considered. The use of fludarabine and alemtuzumab may result in prolonged immunosuppression and subsequent opportunistic infections, for which prophylactic antibiotics may be necessary. For some younger patients with adverse factors, fludarabine/ cyclophosphamide combinations can be indicated. Also, ASCT can be considered.

B symptoms (fever, weight loss or night sweat) can occur during the course of the disease. Sometimes, it may be difficult to differentiate from infections. B symptoms, however, may be an indication for treatment initiation.

Some patients may suffer splenomegaly, resulting in pain, hypersplenism and secondary cytopenias. This may respond to systemic therapy; however, low-dose splenic irradiation may also be considered.

A difficult challenge is the treatment of autoimmune phenomena, such as hemolytic anemia and thrombocytopenia. There is not always a clear correlation with tumor load. Steroid treatment is in many patients beneficial. In addition, especially in cases of high tumor load, antileukemic treatment should be considered.

**malignant lymphomas**

In contrast to the NHLs, Hodgkin’s disease is less likely to disseminate, or in case of dissemination, it has a lymphatic spread. For this reason, these patients are more likely to present with localized disease. This is the reason that historically
radiotherapy has an important role in patients with Hodgkin’s disease. Radiotherapy is a very effective treatment in Hodgkin’s disease; however, the efficacy, of course, depends largely on appropriate staging. Because of the presence of subclinical disease in a subset of patients, chemotherapy is increasingly used and may replace the radiotherapy. This is related with the increasing awareness of secondary malignancies as the result of the combination of radiotherapy and chemotherapy. To find the right balance between the advantages of therapy and the long-term complications, patients with Hodgkin’s disease (especially with localized Hodgkin’s disease) should be treated in well-designed clinical trials. ABVD chemotherapy is considered the standard of care. Clinical trials, however, should assess how many cycles should be given and whether more or less involved field radiotherapy should be part of the treatment. Depending on stage, 60%–90% of the patients with Hodgkin’s disease can be cured. Relapsed patients may benefit from reinduction chemotherapy followed by high-dose therapy and autologous stem-cell transplantation.

Patients with NHL generally present with disseminated disease. Especially patients with low-grade, indolent disease present with stage IV disease. Also, however, patients with low-grade lymphoma and stage IV disease may have no or relatively little symptoms. In these patients wait-and-see policy is justified. In case of symptomatic disease, a combination with rituximab (anti-CD20) and alkylator-chemotherapy (CVP) results in major response rates and, therefore, a higher likelihood of relieving the symptoms. Although not curative, this treatment may result in long-term responses. In case of relapse, the same therapy may be repeated. Patients with follicular lymphoma and a short response on first-line treatment may benefit from high-dose therapy followed by autologous stem-cell transplantation. Nonmyeloablative ASCT may also be an option. Here the chance of cure, however, should be balanced against the potential for treatment-related mortality.

Patients with aggressive lymphoma can be subdivided on the basis of the prognostic factors (IPI score). Patients with low-risk lymphoma respond very well on the combination of chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone + rituximab; patients with high-risk lymphoma benefit from more intensive rituximab containing chemotherapy regimens which may also include high-dose therapy followed by autologous stem-cell transplantation. In case of relapse, patients with chemo-sensitive aggressive NHL still have 50% chance of cure when treated with high-dose therapy followed by autologous stem-cell transplantation. The place of radiolabeled Abs is not yet clear. Some patients may present with marginal zone lymphoma in the stomach. In the majority of cases, Helicobacter pylori can be demonstrated in tumor biopsies. These patients may very likely benefit from eradication therapy for the H. pylori.

T-cell NHL is a relatively rare presentation. Patients can be subdivided in those with a low-grade malignancy generally presenting in the skin, which can be treated with either local therapy, such as psoralen plus UVA and, exceptionally, radiotherapy or surgery. A few patients will present with peripheral T-cell NHL with nodal and extranodal localizations. Generally, these patients will be treated as high-risk lymphomas (without rituximab) but they still will have a poor prognosis when treated with these therapies. Alemtuzumab may be indicated as well in specific cases.

**multiple myeloma**

Patients with multiple myeloma present with disseminated disease. Sometimes, they may have local symptoms due to osteolytic lesions in the bones. These may be treated with palliative radiotherapy.

Treatment is indicated in patients with active myeloma but should be withheld in those with asymptomatic disease. Generally, patients are treated with systemic chemotherapy, where vincristine–adriamycin–dexamethasone (VAD) chemotherapy is the standard of choice. On the basis of the results of French studies, currently high-dose therapy followed by autologous stem-cell transplantation in first-line treatment is the standard of care for those who are physically fit for this procedure. For patients above the age of 60–65 years, this is less clear. High-dose therapy followed by autologous stem-cell transplantation results in a median prolongation of survival with little more than 1 year. In younger patients, ASCT may be considered because it is evident that this treatment modality may result in cure. Advantages, however, have to be balanced against the relatively high treatment-related mortality.

For all other patients, several treatment options exist ranging from single-agent high-dose dexamethasone in good-risk patients to melphalan–prednisone, thalidomide, thalidomide–dexamethasone, thalidomide–dexamethasone chemotherapy to VAD. Recent data show a high response rate (80%) and increased overall survival in patients treated with melphalan–prednisone–thalidomide, making this combination an attractive choice even for elderly patients. Bortezomib and bortezomib–dexamethasone as well as bortezomib–dexamethasone chemotherapy (or thalidomide) combinations are active in heavily pretreated patients and render high response rates (80%–90%) in newly diagnosed myeloma. Recently, lenalidomide, a derivative of thalidomide and member of the so-called IMIDs, has been introduced as an oral drug with high activity.

Patients with multiple myeloma may present with hypercalcemia or spinal cord compression due to osteolytic fractures. For treatment options in these circumstances see the chapter on Emergencies.

**myeloproliferative diseases**

**chronic myeloid leukemia**

The chronic myeloid leukemias (CML) are characterized by the presence of the Philadelphia chromosome (t(9;22). This abnormality results in abnormal tyrosine kinase function in the myeloid cells. This can be corrected by the treatment with imatinib. The standard of care is currently that patients with CML are treated with imatinib (400 mg). In the overwhelming majority of patients, this will result in hematological complete responses. In a significant subset of patients also cytogenetic complete responses can be obtained (complete disappearance of the Philadelphia chromosome). Monitoring of the bcr-abl abnormality in blood is of great importance to assess the
prognosis. It is increasingly clear that patients who have a 3-log response within the first 12 months of imatinib treatment have a better prognosis than patients who do not obtain this response. In the patients with a suboptimal response, increasing the dose of imatinib may help. Novel tyrosine–kinase inhibitors may have value in the near future.

Since decades, ASCT in patients with CML having an HLA-identical donor was the standard of care. The efficacy of imatinib has resulted in a significant decrease of patients being transplanted early in the disease. Future clinical trials should make the position of ASCT in patients with CML clearer. Currently, it may be advised that patients who do not obtain a significant molecular response should be candidates for allogeneic transplantation.

**polycytemia vera**

Patients with polycytemia vera are currently treated with phlebotomy to decrease the hematocrit to <0.45 in male and <0.42 in female patients. From a randomized study, it is now clear that low-dose aspirin should be added, unless patients have signs of hemorrhagic complications. Some patients may develop severe complaints of iron deficiency. In these cases treatment with hydroxyurea instead of phlebotomy may be helpful.

**essential thrombocytosis**

Patients with essential thrombocytosis may present not only with clotting but also with hemorrhagic diathesis. Patients presenting with hemorrhagic disease have a contraindication for aspirin therapy. Patients who present with thromboembolic complications may benefit from aspirin. High platelet counts (>1000) should also be treated with either hydroxyurea or subcutaneous interferon (IFN). It is still debatable whether hydroxyurea treatment results in an increased risk for leukemia. IFN may have significant side-effects which may be better tolerated using PEG–IFN. Anagrelide has been licensed for second-line treatment. Although this drug is very active, a substantial number of patients have to discontinue the treatment because of significant side-effects.

**idiopathic myelofibrosis**

Patients with idiopathic myelofibrosis may present with elevated blood cell counts, which does not need any treatment. During the disease, splenomegaly may develop. If symptomatic, this may respond to hydroxyurea therapy. Sometimes, IFN is also used. Splenectomy or radiotherapy is rarely necessary. In sporadic cases, thalidomide/dexamethasone can be of help. Also, anagrelide may be an option; however, its place is poorly defined.

The disease may develop into a spent phase where supportive care consisting of transfusions is part of the care.

**response evaluation**

Many decisions on treatment in hematological malignancies depend on the response of previous therapy. Therefore, response evaluation is of utmost importance. For this, we refer to chapter 6.