Update on therapies for lymphoproliferative disorders

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Diabetes mellitus as a late effect of the treatment of Hodgkin lymphoma[1]

Two recent follow-up studies of childhood cancer patients who had been treated with abdominal radiation revealed an increased risk of diabetes mellitus (DM) in the survivors. In the past, many patients with a diagnosis of Hodgkin lymphoma (HL) were also treated with infradiaphragmatic radiation. The para-aortic and splenic fields used for this treatment encompasses most of the pancreas, including the tail. Since diabetes is a risk factor for cardiovascular disease, it is conceivable that an increase in diabetes in survivors of HL might contribute to their increased risk of cardiovascular disease.

In this recent study of adults, the results of the treatment of 2,352 Dutch 5-year survivors of HL treatment who were younger than 51 years at the time of diagnosis were analyzed. Detailed records of their treatment and late effects of treatment were obtained, including information about DM, hypertension, hypercholesterolemia, smoking, and obesity. Radiation dose to the pancreas was estimated.

After a median follow-up of 21.5 years, the following conclusion could be reached from this data set:

a) The risk of diabetes was increased compared with the general population if the radiation dose to the pancreas was > 36 Gy.
b) Male gender was associated with an increased risk of diabetes.
c) Patients treated before age 25 years had the least risk compared with older adults.
d) Diabetes occurred in the first decade of follow-up or not at all.

Key points

In this study, the risk of DM was not increased in patients who had been treated with 10-35 Gy of radiation, but was significantly increased with doses greater than 36 Gy, with a 30- year risk of 14.2% in those patients. Only 8% of the patients with DM were obese. Gender did not modify the risk of DM. The risk was higher for patients diagnosed before age 25 years, but the risk was also increased for those aged 25-50 years. The cumulative risk of diabetes was greater after 30 years of follow-up, compared with 20 years of follow-up, and was still increasing after 40 years and beyond. On the basis of this study and others, HL survivors who received abdominal radiation therapy should be screened for DM.

Answer a

RESORT results: end of an era[2,3]

About 20% of patients with follicular lymphoma are treated with single-agent rituximab as initial therapy, and many of those patients receive maintenance therapy, which seems to prolong response duration. However, it isn't clear if this treatment strategy translates into an improvement in long-term disease control. Furthermore, there is significant cost and some toxicity to maintenance therapy (MR) with rituximab. In RESORT (Rituximab Extended Schedule or Re-Treatment Trial), 289 patients with low-tumor burden follicular lymphoma were randomized to receive MR until progression or retreatment with rituximab (RR) at time of progression. The primary endpoint was time to treatment failure, and secondary endpoints were time to first cytotoxic therapy, and health-related quality of life.

After a median follow-up of 4.5 years, the trial yielded the following results *except*:

a) The MR group received more rituximab overall.
b) The 3-year freedom from cytotoxic chemotherapy was statistically higher in the MR group.
c) The time to treatment failure was statistically shorter in the MR group.
d) There was no difference in health-related quality of life.

Key points

The results of the RESORT trial were impressive for how well the patients assigned to RR did overall. The primary endpoint of time to treatment failure was statistically the same as it was for the MR group. Furthermore, the MR group received more

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rituximab than the RR group received. Since the study had the unique design for indefinite MR, IgA and IgM levels decreased by almost 50%, and there was a potential for increased infections as has been observed in other trials. In RESORT, the incidence of infection was the same in both groups. The health-related quality of life was also the same, despite a statistical advantage for the MR group in terms of time to first cytotoxic chemotherapy. Thus, the strategy of RR resulted in the use of less rituximab, with no decrement in time to treatment failure or quality of life. A retreatment strategy is preferable to maintenance therapy.

Answer c

Prognostic value of PET/CT scan during treatment of Hodgkin lymphoma[4]

Although the long-term survival in patients with Hodgkin lymphoma is high compared with other malignancies, the burden of late toxicities in survivors has become a growing concern. A solution to this problem might be effective predictive tests that would allow for more individualized therapies that would limit the overtreatment of some patients. The current study evaluated the usefulness of a PET/CT scan done after one cycle of chemotherapy (PET1).

PET/CT was performed within the last 5 days of the first and second courses of chemotherapy (PET1 and PET2, respectively). The results of the study showed:

a) Neither PET1 nor PET2 were reliable predictors of outcome.
b) PET2 was as predictive of outcome as PET1.
c) PET1-negative patients had a 2-year progression-free survival (PFS) more than twice that of PET1-positive patients.
d) PET1 is no more useful than other prognostic tools that are already available and more cost effective.

Key points

Early and accurate prediction of response in the treatment of Hodgkin lymphoma might allow earlier termination or alteration of treatment, which would prevent overtreatment in some patients and more effective aggressive therapy approaches in others. In this study, PET1 was shown to be the most effective prognostic tool ever tested. PET 2 was not as predictive as PET1, and furthermore, all PET1-negative patients were also PET2-negative.

Answer c

Imaging in the staging and response assessment of lymphoma[5]

Responding to the widespread adoption of PET/CT imaging for staging and response evaluation in patients with malignant lymphoma, an international workshop that was convened in 2011 to evaluate imaging, last reported at the International Conference on Malignant Lymphoma (ICML) in Lugano, Switzerland, in 2013. A consensus report from the conference has recently been published. Representatives from the major international co-operative groups reviewed the literature and current research.

The ICML consensus on imaging agreed on the following uses of PET/CT imaging in the management of lymphoma:

a) PET/CT is the modality of choice for suspected CNS lymphoma.
b) PET/CT may eliminate the need for bone marrow biopsies in Hodgkin lymphoma and aggressive NHL.
c) PET/CT can be used with confidence in lymphomas with low FDG (fluorodeoxyglucose)-avidity.
d) Interim PET/CT done midtherapy allows the treating oncologist to appropriately switch to a more effective therapy.

Key points

PET/CT is now essential in the staging of patients with PET avid malignant lymphoma. PET/CT may obviate the need for bone marrow biopsies in Hodgkin lymphoma and aggressive non-Hodgkin lymphoma (NHL). Central nervous system lymphoma is still best evaluated with MRI scanning. Interval scans are still being evaluate in clinical trials examining "response-adapted" treatment regimens, but firm conclusions are not yet available. Currently, this approach is not the standard of care.

Answer b

Initial evaluation, staging, and response assessment in lymphoma[6]

A workshop held at the 2012 ICML was attended by thought leaders from major co-operative groups and cancer centers from around the world. The intent was to modernize staging and response criteria. This work was followed by the formation of subcommittees for clinical staging and imaging issues, followed by yet another workshop at 2013 ICML.

As a result of the subcommittees and workshops held at the 2012 and 2013 ICML conferences, the following changes in initial evaluation, staging, and response assessment of lymphomas were recommended *except*:

a) The suffixes A and B for symptoms will be dropped from the staging system for NHL, but retained for Hodgkin lymphoma.
b) When a bone marrow biopsy is required, it should be a 2.5-cm unilateral biopsy.

c) Routine surveillance scans during follow-up are not recommended.
d) PET, although helpful in initial staging, is not mandatory, CT alone is adequate and more cost effective.
e) Chest X-ray is not required for initial staging.

Key points

Since the traditional A and B symptoms are not universally recorded, inaccurate, and have no bearing on treatment in NHL, these designations have been dropped from the staging classification except for Hodgkin lymphoma because symptoms still influence therapy in that disease. Bone marrow biopsy is not required in Hodgkin lymphoma and most cases of diffuse large-cell lymphoma. When it is required, a unilateral biopsy of 2.5 cm should be performed; bilateral iliac crest biopsies are not required.

Routine surveillance scans are not required because there has not been an effect on outcome. PET/CT is now a standard part of initial staging in all PET avid lymphomas. Since CT of the chest will always be part of staging, there is now no need for a chest X-ray.

Answer d

Targeted therapy for chronic lymphocytic leukemia[7]

Historically, options for the treatment of chronic lymphocytic leukemia (CLL) were limited and relatively ineffective. However, more recently the development of chemoimmunotherapy has proven to be superior to older single-agent alkylating therapy. New monoclonal antibodies and targeted agents such as ibrutinib and idelalisib have recently been approved. A review of these treatments has recently been published.

Results of recent trials of targeted therapies in CLL have led to the following conclusions:

a) A variety of targeted approaches have now replaced the use of chemoimmunotherapy as initial therapy for CLL.
b) Ibrutinib may soon replace high-dose steroids and alemtuzumab for symptomatic previously untreated CLL with del(17)(p13.1).
c) Unlike ibrutinib, idelalisib does not cause an early lymphocytosis concomitantly with a reduction in nodal size.
d) Ibrutinib is contraindicated in patients using aspirin or other antiplatelet agents.

Key points

Despite the advent of new monoclonal antibodies and targeted therapies, recent trial results in symptomatic, untreated younger patients with IGHV-mutated and favorable cytogenetics indicate that combination chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) is the preferable initial therapy. FCR is superior to bendamustine plus rituximab in fit young patients. For older patients, obinutuzumab plus chlorambucil or bendamustine plus rituximab are the best choices for initial therapy.

For patients with del(17)(p13.1) chemoimmunotherapy is not effective, and until recently, high-dose steroids plus alemtuzumab was recommended. Results with ibrutinib in this unfavorable group of patients has been very promising, and the toxicity is much less. Ibrutinib is contraindicated in patients receiving concomitant warfarin treatment because of a small risk of subarachnoid hemorrhage, but there have been no problems with other anticoagulants or antiplatelet agents. Since Bruton tyrosine kinase may inhibit stable thrombus formation, ibrutinib should be held for 3-7 days before surgical procedures.

Treating physicians should be aware that both ibrutinib and idelalisib can cause a lymphocytosis concomitant with the reduction in lymph node size during the early phase of treatment.

Answer b

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