Current Approaches to Therapy for Indolent Non-Hodgkin's Lymphoma

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Progress in the treatment of indolent non-Hodgkin’s lymphoma has been slow and the disease remains incurable despite the relatively long median survival of patients. Decades of clinical trials resulted in standard

Introduction

Progress in the treatment of indolent non-Hodgkin’s lymphoma has been limited over the past few decades and, despite the relatively long median survival of patients with non-Hodgkin’s lymphoma, this disorder remains incurable. The approach to treatment is generally determined by whether the disease is limited (stage I and non-bulky stage II) or advanced (bulky stage II, stages III and IV). In the 10% to 15% of patients with low-grade non-Hodgkin’s lymphoma who present with limited disease, radiation therapy has generally been recommended because it can produce a 10-year failure-free survival of 50% to 60%, with an overall survival of 60% to 80%.[1] However, whether even limited stage disease is curable by radiation therapy, with or without chemotherapy, is unclear.

A long-term follow-up study from Stanford included 177 patients with stage I and 104 with stage II follicular non-Hodgkin’s lymphoma at a median age of 53 years.[1] Patients were treated with radiotherapy and followed for a median of 7.7 years (the longest being 31 years). The median survival was 13.8 years. Over 10% of patients relapsed, however, after 10 or more years of being in remission.

Seymour et al[2] reported on 91 patients treated with combined modality therapy. The complete response rate was 99% and only 16 relapsed at a median follow-up of 60 months, but with no plateau on the relapse-free survival curve. Whether there is an advantage to initiating radiation therapy at diagnosis in patients with limited stage indolent non-Hodgkin’s lymphoma was examined by Soubeyran et al.[3] They described 26 patients with stage I follicular non-Hodgkin’s lymphoma who were not treated following excision, but were followed for a median of 6.3 years.

At that time, half were still free from recurrence; six relapsed only locally at a median of 4.2 years. Of 27 patients who received involved field radiation alone or with CVP (cyclophosphamide [Cytoxan, Neosar], vincristine [Oncovin], prednisone), there were seven distant relapses. No plateau was apparent on the time-to-relapse curve. Therefore, although long-term disease control is possible, even limited disease may not be curable.

Advanced Disease

Although low-grade non-Hodgkin’s lymphomas are considered to be “indolent” tumors, the median time to progression in patients with advanced stage disease is 4 to 6 years, with an overall survival of 6 to 10 years.[4-6] Portlock et al[7] performed a retrospective analysis of 44 nonprotocol patients for whom therapy was deferred and compared their outcome to that of 112 previously untreated patients entered into prospective Stanford clinical studies. The median time to starting treatment for the 44 patients was 31 months, with 19 not needing treatment for as long as 104 months. The 4-year actuarial survival for the two groups did not differ.

In a study from the Groupe D’Etude des Lymphomes Folliculaires (GELF).[8] patients with a low tumor burden were randomized to observation, alpha-interferon, or prednimustine (Sterecty). There was no difference in survival among the groups. At the National Cancer Institute, patients were randomized to observation alone or ProMACE/MOPP (prednisone, methotrexate [Rheumatrex],...
leucovorin, doxorubicin [Adriamycin], cyclophosphamide, etoposide [VePesid] and mechlorethamine [Mustargen], vincristine, procarbazine [Mutalone], prednisone chemotherapy). Those who achieved a complete response received total lymphoid irradiation. There is still no difference in survival with more than 13 years of follow-up (D. Longo, 2nd International Symposium on Malignant Lymphomas, Munich, 1998).

Since there is no apparent advantage to early intervention in patients with advanced stage disease, the decision to treat is generally based on the presence of increasing adenopathy, organ compromise, bone marrow failure, or constitutional symptoms. At the time these symptoms appear, the therapeutic options range from administering a single alkylating agent or a combination regimen (eg, CVP), to more aggressive approaches, with no clear evidence of a survival advantage for one treatment over the others. Even the frequency of complete responses with the same or different programs varies widely among series, reflecting differences in patient selection, and staging and evaluation techniques.

In an Eastern Cooperative Oncology Group (ECOG) trial,[4] there was no difference in complete response rates or survival duration with chlorambucil (Leukeran) and prednisone (CP), CVP plus procarbazine (COPP), or carmustine (BCNU) (BCVP), and no plateau of the time-to-progression curves. Other intensive regimens have failed to demonstrate benefit over less intensive programs. An early nonrandomized study in which more intensive therapy appeared to benefit patients with follicular mixed non-Hodgkin’s lymphoma compared with follicular small-cleaved cell non-Hodgkin’s lymphoma[9] was not confirmed.[6,10]

In an analysis of Southwest Oncology Group (SWOG) trials using cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) to treat indolent histologies of non-Hodgkin’s lymphoma, the median durations of response and survival were no better than generally observed with a single alkylating agent.[6] The Lymphoma Group of Central Sweden randomized 259 patients to chlorambucil and prednisone or CHOP—CHOP achieved a higher response rate, but with no difference in survival.[11]

**Relapsed and Refractory Disease**

Relapse with low-grade non-Hodgkin’s lymphoma is inevitable. Although patients often respond again to the same or a similar induction regimen, the quality of their response becomes worse and the duration shorter. In a series from St. Bartholomew’s Hospital,[5] the response rate progressively decreased from 78% after first relapse to 48% after the fourth treatment, and the median duration of first remission was 31 months, compared with only 13 months for second remissions. The median survival following recurrence was 4 1/2 years with only eight of the 116 patients with recurrent disease dying of unrelated causes.

In another series, the median survival following relapse after an initial complete remission of a year or longer was only 5.9 years; median survival was 4.2 years after a partial response of at least a year, but only 2.4 years after an initial response shorter than a year.[12] Whereas most patients recur with a similar histology, there is a constant risk of undergoing a transformation to a high-grade non-Hodgkin’s lymphoma—generally considered an ominous event. If diagnosed and treated early, however, a small proportion of patients with transformed non-Hodgkin’s lymphoma may experience prolonged disease-free survival.[13]

A variety of aggressive combination regimens have been used to treat relapsed or refractory patients,[14-20] with no evidence of a major advantage from any of them.

**New Treatment Approaches**

New approaches being evaluated to improve the outcome of patients with advanced low-grade non-Hodgkin’s lymphoma include new chemotherapy agents, biological therapies, and dose intensity with either allogeneic or autologous stem cell support.
New Chemotherapy Agents

The most interesting new agents are those with unique mechanisms of action. The most promising of those include the purine analogs fludarabine (Fludara), cladribine (2-chlorodeoxyadenosine, CdA) (Leustatin), and pentostatin (2′-deoxycoformycin, DCF) (Nipent) (Table 1). Fludarabine and CdA are of particular interest because they induce apoptosis of lymphocytes, which has been implicated in the pathogenesis of indolent lymphoid malignancies.

Fludarabine

Responses to fludarabine occur in about half of patients with an indolent non-Hodgkin’s lymphoma who have relapsed following an initial response or who are refractory to prior therapies, including 10% to 15% complete remissions (Table 1).[21-27] Redman et al.[21] used a dose of 25 mg/m² for 5 days to treat 67 patients who had received a median of three prior regimens. The overall response rate was 55% for patients with a low-grade histology. The overall median time-to-treatment failure of 7.5 months also applied to patients with an aggressive histology—it is not possible to separate the outcomes of indolent non-Hodgkin’s lymphoma from that of aggressive tumors.

Eastern Cooperative Oncology Group investigators[22] reported on 62 assessable patients with relapsed and refractory non-Hodgkin’s lymphoma, including 27 with a low-grade histology. Fludarabine was administered at a dose of 18 mg/m² daily for 5 days. The overall response rate for indolent histologies was 52%, and the median survival of responders was in excess of 30 months. Of the nine complete responders, four remained in continuous remission, three for longer than a year after completion of therapy. Other published series confirm these results.[23-25, 27]

Complete remissions are more common in patients who receive fludarabine as initial treatment for an indolent non-Hodgkin’s lymphoma, with a frequency of almost 40%, and an overall response rate of about 70% (Table 2).[23,25,28] In a report of 53 patients from the French Groupe d’Etude des Lymphomes de l’Adulte (GELA), the median time to progression was 13.6 months, with a relapse-free survival of 15.6 months.[28] Pigadiou et al.[23] reported a complete response rate of 38% in the indolent histologies, but did not project response duration. Although randomized trials comparing fludarabine with alkylating agent-based regimens as initial treatment have not been completed in non-Hodgkin’s lymphoma, fludarabine clearly offers an effective alternative to alkylating agents (Figure 1).

Fludarabine Combinations

Unfortunately, despite the high complete response rate with fludarabine, relapse is inevitable. This failure to cure patients has led to the development of combination regimens. Fludarabine interferes with the DNA repair following exposure of cells to a variety of DNA damaging agents, including radiation, topoisomerase II (TPII) inhibitors, and alkylating agents. Therefore, this drug has been combined with the TPII inhibitor mitoxantrone (Novantrone).[45-47]

McLaughlin et al.[45] reported on a phase I trial in 21 refractory and relapsed patients. Responses were observed at each dose level, with a complete response rate of 43% and an overall response rate of 71%. The median duration of the complete responses was 18 months. The dose-limiting toxicities were neutropenia and infection. In their subsequent phase II study,[46] 51 patients were treated with fludarabine at 25 mg/m² daily for 3 days, mitoxantrone at 10 mg/m² on day 1, dexamethasone 20 mg on days 1 to 5, and two double-strength trimethoprim sulfamethoxazole tablets twice weekly.

Courses were repeated every 4 weeks for a maximum of eight cycles. This regimen yielded a response rate of 94%, with 47% complete remissions. The median failure-free survival was 14 months—21 months for complete responders and 9 months for partially responding patients. The median survival for the group was 34 months.

Zinzani et al.[47] treated 48 patients with the fludarabine, Novantrone, dexamethasone (FND) combination. The histologies of this group included 30 follicular non-Hodgkin’s lymphomas and 18 immunocytomas. The complete response rate was 35%, with 48% of patients responding partially.
Relapse-free survival projected at a median follow-up of 15 months was 32% for complete responders and 18% for partial responders. The Southwest Oncology Group performed a confirmatory trial of this regimen as front-line therapy, omitting dexamethasone, and the results are undergoing analysis.

Younes et al[48] conducted a phase I trial of fludarabine and paclitaxel (Taxol). The maximum tolerated dose was fludarabine at 20 mg/m² daily for 5 days and paclitaxel at 60 mg/m²/day as a 73-hour infusion. The dose-limiting toxicity was neutropenic fever. Stomatitis, neuropathy, and hypotension were also noted at the highest dose level. Overall, 50% of patients responded, and 62% of those had no prior exposure to either agent.

The Eastern Cooperative Oncology Group recently updated the results of their study of the combination of cyclophosphamide at 1,000 mg/m² on day 1, with fludarabine 20 mg/m² for 5 days given monthly in 27 previously untreated patients.[49-51] This program achieved a 100% response rate including 89% complete responses. At a median follow-up of 53+ months, the median time to failure was 56 months, with 14 patients remaining in continuous complete remission. This combination is currently being compared to cyclophosphamide, vincristine, and prednisone in a front-line ECOG study of indolent non-Hodgkin’s lymphoma, with a secondary randomization for responders to either maintenance therapy with rituximab (IDEC-C2B8 [Rituxan]) or observation.

Fludarabine has also shown impressive activity against Waldenström’s macroglobulinemia (Table 2). Kantarjian et al[52] first evaluated fludarabine in 11 patients, all but one of whom had failed prior therapy. At least a 50% decrease in IgM was achieved in 45%, lasting a median of more than a year. Dimopoulos et al[53] updated those data with 28 patients, of whom only two had not received prior therapy. After a median of three courses of drug, the response rate was 36%, lasting a median of 38 months. Zinzani et al[54] reported a 41% partial response rate in 12 previously treated patients.

Recently, the Groupe Coopératif Macroglobulinémie reported on 82 heavily pretreated patients, 63 of whom were evaluable for response. The median age was 68 years, and they had received a median of two prior regimens. A decrease in IgM by more than 75% was noted in 30% of patients, and a 50% decrease was noted in an additional 25%. A current European trial is comparing fludarabine with CAP (cyclophosphamide, Adriamycin, and prednisone).

**Cladribine**

Cladribine is also active in indolent non-Hodgkin’s lymphoma (Table 1). Kay et al[29] reported on 40 patients who had failed a median of three prior regimens for an indolent non-Hodgkin’s lymphoma, and noted a complete response rate of 20%, with a partial response rate of 23%. The median duration of response was 5 months (6 months for the complete responses). Grade III or IV neutropenia was encountered in 18% of patients, and grade III or IV thrombocytopenia in 30% of patients. Hoffman et al[31] described their results with 21 patients; responses included 13% complete responses and 30% partial responses. Two of the three patients who achieved complete responses relapsed at 6 months, while the third was reported to be in remission at 23+ months.

Half of the courses were associated with grade III or IV neutropenia, 32% of patients experienced febrile neutropenia, and 29% died of infection. Betticher et al[32] reported responses in 75% of 16 patients with indolent non-Hodgkin’s lymphoma, including complete responses in 19%. Complete responses were not observed in intermediate- or high-grade non-Hodgkin’s lymphoma. The median duration of response was only 3+ months.

Robak et al[34] described 94 patients who received cladribine as a 2-hour infusion for 5 days resulting in death in three patients, complete responses in 12.8%, and partial responses in 38.3%. In a multicenter study,[35] 104 patients received either the standard 0.7 mg/kg or a reduced dose of 0.5 mg/kg. Response rates were similar in the two arms (15% complete response and 39% partial response), with a median response duration of 9 months. The risk of infection was reduced by 81% using the lower dose.

Cladribine achieves responses in more than 70% of previously untreated patients, including 20% complete response.[36,37,39] Saven et al[36] described 28 patients who received a median of three
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Published on Physicians Practice (http://www.physicianspractice.com)

courses of cladribine. Of 26 who were evaluable for response, 35% attained complete response, and 54% had partial response, but with a median duration of response of only 10 months. In a preliminary report of a Cancer and Leukemia Group B (CALGB) study, 31% of patients achieved complete response, with the remainder achieving partial response. Half of the patients had already relapsed by 15 months.

Betticher et al.[39] recently reported 14% complete and 70% partial responses in 37 patients with previously untreated non-Hodgkin's lymphoma. The median time-to-treatment failure was 15.7 months. However, almost a third were unable to complete the planned five courses because of progression or toxicity. The investigators concluded that this treatment was no better than standard therapy, but was more toxic.

Rummel et al.[40] presented 47 patients, 38 of whom had a low-grade histology, and nine others with mantle-cell non-Hodgkin's lymphoma. The complete response rate in the low-grade histologies group was 37% with 42% partial response. In the group of nine patients with mantle-cell non-Hodgkin's lymphoma patients, there was one complete response and three partial responses. No response duration was provided. Canfield et al.[38] reported 14 patients who received a median of 3.5 months of therapy. The overall response rate was 71%, but with only 7% complete response.

Cladribine has also shown promise in patients with Waldenström's macroglobulinemia (Table 2). Dimopoulos et al.[56] treated 46 patients who were resistant to alkylating agents and observed 43% responses, with a median progression-free survival of 12 months. The same investigators[53] treated 29 symptomatic patients, including nine who were newly diagnosed, four who relapsed off therapy, nine who had primary refractory disease, and seven who were in refractory relapse. There were 59% partial responses. With a median follow-up of 7 months, one patient had relapsed.

They also reported that almost half of patients responded to cladribine as primary therapy for macroglobulinemia [58]. At a median follow-up of 13 months, there were 5 relapses and all who were retreated responded again. Betticher et al.[57] treated 25 previously treated patients with subcutaneous injections of cladribine. There were no complete responses, and 40% partial responses, a median time-to-treatment failure of 4.4 months, and a median remission duration of 8 months.

There is limited experience with cladribine in combination with other drugs[59, 60] and the data do not appear to support superior performance to cladribine alone in comparable patients.

**Pentostatin**

The published data with pentostatin (DCF) in non-Hodgkin's lymphoma are limited and difficult to interpret.[41-43] Cummings et al.[43] reported an ECOG trial of 37 patients treated with 5 mg/m² for 3 consecutive days every 3 weeks. Of seven patients with a low-grade non-Hodgkin's lymphoma, there were two responses. There were four fatal toxicities, two from infections and two from cardiac causes. Duggan et al.[41] described 76 patients in a CALGB trial using DCF 4 mg/m² weekly for 3 weeks, then every other week for a minimum of 5 treatments. Five of the 24 patients with a low-grade histology responded. Responses have also been reported in other chronic lymphoid malignancies.[43, 61]

**Toxicities of Purine Analog Therapy**

Major side effects of fludarabine, cladribine, and DCF include moderate myelosuppression, profound immunosuppression, and neurotoxicity.[62,63] Febrile neutropenia occurs in about 20% of patients treated with fludarabine, and in 30% to 50% of cladribine-treated patients. Lymphocyte counts decrease within a couple of weeks following administration of these drugs.

Primarily affected are CD4 cells that decrease to levels expressed in patients with AIDS and that may remain depressed for a year or longer following fludarabine, and perhaps even longer following cladribine or pentostatin.[63-66] A consequence of this effect is an increased risk of opportunistic infections, made worse with concurrent steroids.[66]
Although prophylactic antimicrobial therapy or intravenous immunoglobulins have been recommended by some physicians, this approach is costly, potentially toxic, and cannot cover the range of possible organisms.[63] An additional consequence of the severe, prolonged immunosuppression may be an increase in secondary malignancies.[67]

Tumor lysis syndrome occurs in fewer than 1% of patients.[68] It is not routinely preventable, and while often reversible, it is occasionally fatal. Other side effects such as nausea, vomiting, or alopecia are uncommon and generally not severe.[69]

**Other New Agents**

A number of newer purine analogs have entered clinical trials, but the data in lymphomas are limited. Gemcitabine (2’,2’-difluorodeoxycytidine) (Gemzar) is a deoxycytidine analog with structural and metabolic similarities to cytarabine. This drug has been approved by the FDA for the treatment of pancreatic cancer. Santoro et al[70] treated patients with either Hodgkin’s disease or aggressive non-Hodgkin’s lymphoma who failed up to three prior regimens with gemcitabine. Of 14 patients with Hodgkin’s disease, there were 21% complete responses and 36% partial responses, lasting a median of 8 and 6 months, respectively. There were two treatment-associated deaths. Of 22 patients with aggressive non-Hodgkin’s lymphoma, 9% achieved partial response, and five died. There were no patients with indolent non-Hodgkin’s lymphoma in that series.

Compound 506U is a water-soluble prodrug of arabinosylguanine (araG), that is converted to araG by ADA. It is cytotoxic to malignant T cells in vitro and in murine systems. In a preliminary report of a phase I clinical trial in 40 children and adults,[71] there were 15 evaluable patients with T-ALL, 10 of whom had relapsed after bone marrow transplantation, nine of whom achieved a complete remission, and three a partial remission. Of six adults with T-non-Hodgkin’s lymphoma, there was one complete response and five partial responses.

A patient with T-CLL achieved a partial response, and two of six patients with B-lineage CLL responded. Eleven responding patients had not progressed between 2 and 14 months. The dose-limiting toxicity appears to be neurologic. This exciting new compound is currently being explored in additional clinical trials.

The topoisomerase I inhibitors topotecan, irinotecan (CPT-11 [Camptosar]), and 9-aminocamptothecin appear to be active with approximately 25% response rates that vary with histology, dose, and extent of prior therapy. Additional studies are being conducted.[72-75] The taxanes have limited activity in indolent non-Hodgkin’s lymphoma.[76-79]

Other new and interesting chemotherapy drugs in clinical trials include the protein kinase C inhibitors bryostatin,[80] and UCN-01. Flavopiridol which induces apoptosis and inhibits a variety of kinases, including cyclin D1 is, therefore, being studied in patients with mantle-cell non-Hodgkin’s lymphoma.[81] Unlike most chemotherapy agents, these drugs are active in vitro in the setting of p53 mutations.

**Biological Therapies**

**Interferon**

Of the biological therapies available, alpha-interferon (IFN) has been the most widely used (Table 3). Nevertheless, the role of this drug remains unclear.

There are at least 10 randomized trials in which IFN has been used during induction, as maintenance, or as both. When incorporated into induction programs, the effect on response rates has been inconsistent. Some studies using alkylating agent-based regimens have reported a prolongation of time to progression with no prolongation of survival, however.[90-94]

Of the studies combining IFN with chemotherapy agents such as an anthracycline or mitoxantrone[82-84,87,88] there was a longer time-to-treatment failure with IFN in most, but with an
inconsistent effect on survival (Table 3). The Group d'Etude des Lymphomes folliculaires group[84] studied 242 evaluable patients with follicular non-Hodgkin's lymphoma with high tumor burden who were treated with doxorubicin, cyclophosphamide, teniposide (Vumon), and prednisone for a year either alone or with concurrent IFN up to 18 months. The response rate (85% vs 69%), event-free survival (34 months vs 19 months), and overall survival at 3 years (86% vs 69%) all favored the group that received IFN. These results remained significant with additional follow-up.[85,86]

Most of the above trials as well as 1,756 newly diagnosed patients were included in a recent meta-analysis.[95] The four trials that added either an anthracycline or mitoxantrone showed no clear role for IFN in improving the response rate. There was, however, a significant survival advantage limited to complete responses or partial responses in favor of IFN with a 14% advantage at 5 years and a 19% advantage at 8 years. In a SWOG study not included in this analysis,[89] 571 patients received ProMACE/MOPP, with involved field radiation to convert partial responses to complete responses, and responders were randomized to IFN or observation. There was no difference in progression-free survival or overall survival. The explanation for this discrepancy is not clear but may reflect differences in prognostic features or other factors.

Monoclonal Antibodies

Monoclonal antibodies evaluated in the treatment of non-Hodgkin's lymphoma include those that are unconjugated, or linked to an immunotoxin or radioisotope. Recent data with a chimeric anti-CD20 antibody, IDEC C2B8, (rituximab [Rituxan]) in 166 patients showed a response rate of 46% with 8% complete responses. The median time to progression was not reached with 9+ months of follow-up. Rituximab was recently approved by the FDA for the treatment of relapsed follicular non-Hodgkin's lymphoma.[96-100] The drug is well tolerated and courses can be repeated with 40% of patients responding a second time.[101] Current trials are incorporating this agent into chemotherapy combinations.

In a recent intergroup trial, the immunotoxin B4-blocked ricin was unable to prolong disease-free survival when administered following autologous stem-cell transplantation.[102]

Promising results have been reported with several radioimmunoconjugates. Response rates with an 131I anti-CD20 in patients with a relapsed or refractory indolent non-Hodgkin's lymphoma have been greater than 70%, most being complete responses, [103-105] that last from a few months to several years. In a preliminary analysis of 60 previously untreated patients, all 21 who were evaluable responded with 71% complete response; four of 12 polymerase chain reaction (PCR) positive patients became persistently PCR negative.[106] Antibodies conjugated with 90Y have also shown promise.[107, 108]

Other Biological Therapies

Results with an anti-idiotype vaccine from the Stanford group[109] have been updated[110] with long-term follow-up on 41 patients (12 in complete response and 20 with residual disease following chemotherapy). The median freedom from disease progression and overall survival were significantly longer in the 49% who generated a specific immune response than in the responders. Further studies are ongoing. Encouraging preliminary results have been reported with a BCL-2 anti-sense oligonucleotide.[111]

Stem-Cell Transplantation (SCT)

There are limited data available on the use of allogeneic bone marrow transplant in indolent non-Hodgkin’s lymphoma. The reasons for this lack of information include: the lower likelihood of a donor, the greater morbidity and mortality from allogeneic compared with autologous stem cell transplantation, and the relatively long natural history of the disease. The cases in the literature are scattered among a number of series, including a variety of histologies.[112,113]

In a paper from the M. D. Anderson Cancer Center,[114] 10 patients with refractory and relapsed low-grade non-Hodgkin’s lymphoma were transplanted over a 5-year period. Five of these had
primary refractory disease. Eight of the 10 achieved a complete response, with no relapses at a median follow-up of 816 days. However, two of the 10 died of treatment-related complications.

In an analysis of the data from the International Bone Marrow Transplant Registry,[115] there were 81 patients transplanted at a median age of 41 years—56% had never achieved a complete remission. The projected survival at 3 years was 46%, with a 43% disease-free survival. The median follow-up was 23 months. Transplant-related mortality was 44%. These numbers were considered better than with other salvage approaches. However, chemosensitivity is the strongest predictor of outcome.

The experience with autologous stem-cell transplantation for low grade non-Hodgkin’s lymphoma is larger than bone marrow transplantation. Investigators from the Dana-Farber Cancer Center in Boston[116] reported 51 patients who were in a second or subsequent complete remission, or in a state of minimal residual disease (< 2 cm). Thirty-two patients remained event-free from 3 to 60 months with a projected event-free survival of 53% at 4 years.

In a subsequent study,[117] patients became eligible to enter at the time of their first complete response or partial response with minimal residual disease. Of the first 78 patients, there were two treatment-related deaths. Twenty-six patients remained in complete response beyond 2 years with a median duration of remission of 22 months, but with no plateau on the time-to-progression curve. There were 23 relapses and the median time to relapse was approximately 1 year at a median follow-up of only 2 years.

The group from St. Bartholomew’s Hospital[118] reported on 64 patients who received high-dose chemotherapy with purged autologous bone marrow during second or subsequent remission, and were followed for a median of 3 ½ years. Twenty-four patients had relapsed whereas 35 remained in continuous complete remission from 1 to 8 years. When compared with their institutional historical controls, there was a significantly longer time to progression, although without a prolongation of survival.

The data from the Dana-Farber group provide an instructive lesson. Patients who were treated at a time of minimal residual disease and achieved a molecular complete response initially appeared to have a sustained disease-free survival. However, in their more recent follow-up, the appearance of this curve has changed such that there is no longer a plateau.[119]

Short-term and long-range complications of autologous stem-cell transplantation include treatment-related mortality, prolonged anemia or thrombocytopenia, a markedly increased rate of secondary myelodysplasia, and AML which ranges from 6.8% to 19%.[120-122]

When bone marrow transplantation and autologous stem-cell transplantation are compared, the long-term survival figures are relatively comparable. Autologous stem-cell transplant is accompanied by a greater likelihood of dying from disease recurrence, whereas bone marrow transplantation results in a high frequency of death from graft-vs-host disease (GVHD), infection, and veno-occlusive disease. On the other hand, there may be some benefit from a moderate amount of GVHD in the form of graft-vs-lymphoma effect.

**Conclusions**

We are in an exciting time in the treatment of patients with low-grade non-Hodgkin’s lymphoma. The progress in therapy that occurred during the 1960s has reached a plateau in recent years. Decades of clinical trials were devoted to developing empirical combinations of standard chemotherapy drugs to form innumerable similar combinations with virtually identical activity. Clinical drug development focused on the identification of more effective and less toxic analogs of active drugs, but with limited success.

Nevertheless, two events occurring simultaneously in recent years should give us great optimism for future therapeutic progress. First, there has been a remarkable increase in our understanding of the biology and immunology of lymphoid malignancies. Second, we now have a large number of new and
unique chemotherapeutic and biological agents entering into clinical trials. Continued progress towards curing these diseases requires close collaboration between the laboratory scientist and the clinical researcher and, most importantly, referral of patients to high-quality, innovative clinical research trials.

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