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PEDIATRIC HODGKIN'S DISEASE—UP, UP, AND BEYOND

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Juan A. del Regato, 1909–1999, was a superb clinician-educator who recognized the radiocurability of Hodgkin's disease but questioned treatment without late effects, particularly in children. The remarkable progress in pediatric Hodgkin's disease today is a tribute to this influential pioneer, who served as a role model to many. Combined modality therapy using low-dose, involved-field radiation and multiagent chemotherapy today results in a 5-year relative survival rate of 94% among American children with Hodgkin's disease. However, several areas hold promise for future advances, including a new pathology classification and biology studies that distinguish classic Hodgkin's disease from other lymphomas; new noninvasive staging techniques, including 18F-fluorodeoxyglucose-positron emission tomography; the definition of risk groups to segregate low-, intermediate-, and high-risk groups on the basis of a prognostic index, facilitating risk-adapted therapy; and myeloablative therapy followed by hematopoietic stem cell transplantation. Currently used for children with relapse, it is associated with a 5-year survival of 65% and should be considered as the initial therapy for high-risk groups. Idiopathic diffuse pulmonary toxicity after autologous transplantation is high among children with an atopic history; thus, atopy should be considered when selecting children appropriate for transplantation. Finally, novel therapies, such as the anti-CD20 antibody, rituximab, may be useful for children with CD20+, lymphocyte-predominant Hodgkin's disease. The universal goal of cure without late effects is realistic for almost all children with Hodgkin's disease today. © 2002 Elsevier Science Inc.

Pediatric Hodgkin's disease, Treatment, Prognosis.

A TRIBUTE TO A GREAT LEADER

Tributes made to Juan Angel del Regato shortly after his death chronicled the milestones in the life and career of this remarkable pioneer, role model, and leader (1, 2) (Fig. 1). Juan A. del Regato was born in Camaguey, Cuba on March 1, 1909, educated at the University of Paris, and received specialized training in radiation oncology at the Curie Foundation and Radium Institute of the University of Paris. He immigrated to the United States to direct the radiotherapy service at Ellis Fischel Cancer Center in Columbia, MO, and then at the Penrose Cancer Hospital in Colorado Springs, CO. He retired as a Distinguished Physician of the Department of Veterans Affairs in Tampa, FL, and died June 12, 1999.

Dr. del Regato was a superb clinician-educator who influenced many students and colleagues. He served as a role model and mentor to many of today's leaders in radiation oncology, some of whom trained with del Regato at the Penrose Cancer Hospital, and all of whom read his textbook "Cancer—Diagnosis, Treatment, and Prognosis." It was in the fourth edition of this text, published in 1970, in which Dr. del Regato acknowledged that "Hodgkin's disease is radiosensitive and locally radiocurable," but he was concerned about treatment-related toxicity, particularly in chil-

dren. He wrote, "Since patients with Hodgkin's disease are frequently young and may be expected to survive for many years, irradiation should be conducted over a reasonably long period of time to minimize the untoward effects of radiation over the irradiated normal structures" (3). He warned that "Irradiation, even in moderate doses, is fraught with definite hazards in the irradiation of normal structures, such as the lung, spinal cord, heart, and pericardium" (3). Dr. del Regato advocated a conservative approach. He taught that cure of Hodgkin's disease was indeed a possibility, but acknowledged that cure was difficult to define. In his 1970 text, he quoted Vera Peters' data of 1966 in which she reported, "The median survival of all cases with Hodgkin's disease is 34 months" (4). Dr. del Regato emphasized that adequate radiotherapy often results in long survival times, and that, "At least one patient out of every four may live in comfort for 25 years." (3) Many of his students and readers of this 1970 text wondered if Hodgkin's disease really was curable.

This historical perspective is particularly valuable when one acknowledges the revolutionary progress made in pediatric Hodgkin's disease since del Regato's earliest writings. Its usefulness is especially obvious when one imagines what we may foresee in the future for children with

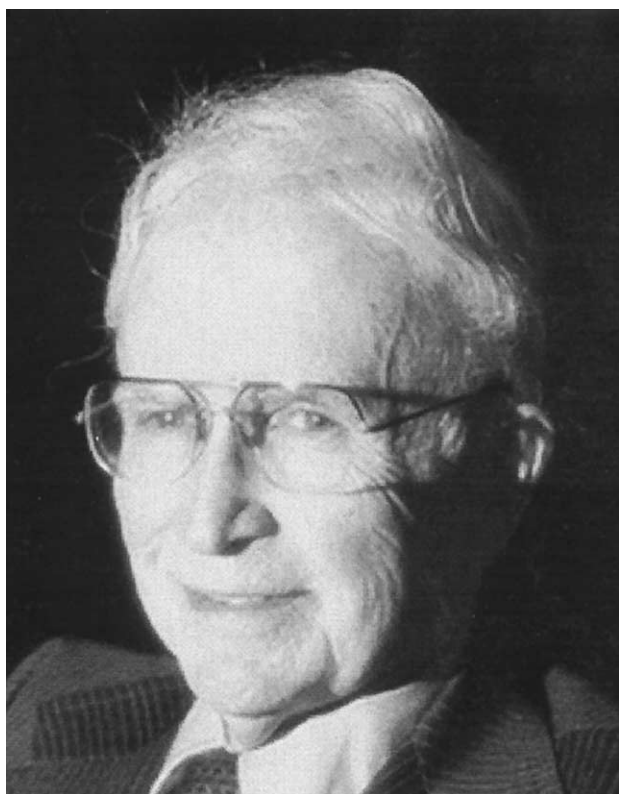


Fig. 1. Juan Angel del Regato, M.D., 1909–1999. From *Int J Radiat Oncol Biol Phys* 1999;45:1, with permission.

Hodgkin's disease—beyond the status we understand today.

LEARNING FROM THE PAST

Changes in the management and treatment of Hodgkin's disease during the past three decades have come in a stepwise progression. In the 1960s, radiotherapy alone was the sole treatment for children with Hodgkin's disease. It required surgical staging and high doses of radiation in the range of 35–44 Gy. By the late 1960s, chemotherapy, using mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) (5), was developed and ultimately newer combinations of drugs were used. During this pioneering time, a focus began on the late effects of treatment, such as the soft tissue and bone growth problems associated with high doses of radiation (6), which were particularly pronounced in young children.

The recognition of late effects from high-dose extended field radiation ushered in a new experience using chemotherapy alone. The first report using chemotherapy alone, six cycles of MOPP, came from Uganda, where no radiation therapy facilities were available (7). The Australian, Cape Town, and Dutch colleagues (8–10) gave 6–12 cycles of chemotherapy for favorable patients with nonbulky disease and/or used supplemental radiation for bulky disease. These limited experiences comprised relatively small numbers of patients, and the reports revealed 5-year survival rates in the

range of 90% for early-stage patients, but 5-year disease-free survival rates of only 40–55% for those with advanced-stage disease. These experiences pointed to the need for conducting prospective randomized trials and the value of combined-modality therapy.

The novel approach of using less-than-standard doses of radiation and experimental MOPP chemotherapy in children paved the way for a broad interest in combined-modality therapy for children (11). This approach of a reduced radiation dose and field size combined with a reduced number of cycles and reduced duration of chemotherapy using less toxic agents offered the opportunity for cure without the late effects observed after high-dose radiation alone or multiple cycles of aggressive chemotherapy. The experiences from Stanford revealed a relapse-free survival rate at 20 years of 85% after 15, 20, or 25 Gy and six cycles of MOPP in surgically staged children (12). Thereafter, the Toronto investigators extended this approach to clinically staged children and reported a 10-year relapse-free survival rate of 80% with 20–30 Gy and six cycles of MOPP (13). Soon the combined modality approach was advanced further by the Intergroup Hodgkin's Disease Study to the use of involved field radiation and MOPP chemotherapy, which revealed a disease-free survival rate of 90% for children with surgical Stage I–II disease (14). This enthusiasm led the French and Italian investigators to use chemotherapy and radiation in doses of 20–25 Gy; the German collaborators used 35, 30, or 25 Gy and two, four, or six cycles of chemotherapy in a risk-adapted approach. All reported disease-free survival rates between 80% and 95% (15–18).

When reports of male infertility and myelogenous leukemia attributed to alkylating agent chemotherapy were reported (19–22), oncologists were quick to substitute the doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) combination (23) in addition to, or in place of, MOPP, as non-cross-resistant drug therapy to be used with low-dose involved-field radiotherapy.

The Stanford investigators reported an overall survival rate of 96% and a freedom from relapse rate of 92% with 15–25 Gy and six cycles of ABVD/MOPP (24). Similarly, the International Society of Pediatric Oncology investigators showed the equivalence of four cycles of MOPP and two cycles of MOPP/two cycles of ABVD when used with 20–40 Gy (15). The Italian National Study then used three cycles of ABVD and 20–25 Gy for Stage I–IIA nonbulky disease, and the Milan Pediatric Group investigated three vs. six cycles of ABVD with 25 Gy for children with Stage I–III disease (16). Although optimistic disease-free survival and overall survival data were reported, gradually the dose-related risks of pulmonary and cardiac injury associated with bleomycin and doxorubicin in the ABVD combination became a concern (24–27).

The commitment to combined modality therapy using low-dose radiotherapy and chemotherapy then required a search for nontoxic chemotherapy, equally as effective as MOPP and ABVD, but with fewer subacute and chronic sequelae. The German Pediatric Oncology Group had ex-

cellent results with their combination of vincristine, procarbazine, prednisone, and doxorubicin/cyclophosphamide, vincristine, procarbazine, and prednisone (OPPA/COPP), with disease-free survival rates of 98–86% (17). However, when they attempted to omit procarbazine, using an OPA rather than OPPA combination, and substituted methotrexate, using a COMP rather than a COPP combination, they observed poorer disease-free survival rates of 85–49% (28). The German investigators then substituted etoposide (VP-16) as OEPA in their next study (29), and the French combined vinblastine, bleomycin, etoposide, and prednisone (VBVP) with or without OPPA for early-stage disease (30). In the United States, the Stanford, Dana Farber, and St. Jude investigators tried vinblastine, etoposide, prednisone, and doxorubicin (VEPA) for children with unfavorable and advanced-stage disease (31). The German OEPA with radiation combination for Stage I–IV gave a 95–84% 5-year event-free survival (EFS) rate, and the French observed a 78–91% 5-year EFS rate using VBVP with or without OPPA with 20-Gy radiation. The Stanford investigators discontinued their VEPA and radiation study when the 2-year EFS was only 60% (31). It appeared that etoposide might be useful as combined-modality therapy for early-stage, but not advanced-stage, disease.

The reality of cure and the concerns over late effects demanded prospective randomized trials to investigate combined-modality therapy vs. chemotherapy alone in clinically staged children. There have been two important American studies. The Pediatric Oncology Group 8725 trial of 183 children with advanced-stage Hodgkin's disease used eight cycles of alternating MOPP/ABVD with or without 21-Gy total lymphoid irradiation (32). Although no difference in 5-year EFS was found when analyzed by an intent to treat, the EFS rate at 5 years of 79–80% was inferior to that reported by others, and the study was criticized for problems in design, analysis, and reporting (33). When the data were analyzed by the treatment actually delivered, an EFS advantage was found for children receiving the combined-modality therapy, and the Pediatric Oncology Group investigators continued to use combined-modality therapy in their next study (34). Similarly, the Children's Cancer Group 5942 trial enrolled 829 children and used risk-adapted chemotherapy with COPP/ABV for Stage I–III patients, adding cytarabine/etoposide for Stage IV patients (35). Children achieving a complete response to chemotherapy were then randomized to receive, or not receive, 21 Gy of radiation. This randomized study was stopped early, when the 3-year EFS was significantly better for the group randomized to the combined-modality therapy. The differences observed were apparent for each individual risk group, as well as for the group as a whole. The improvements favoring the irradiated children were even more impressive when the data were analyzed by the treatment actually delivered. Thus, these American randomized studies continue to support the value of combined-modality therapy using low-dose radiation and multiagent chemotherapy to give the best outcome.

LEARNING IN THE PRESENT

The multi-institutional, multinational commitment to combined-modality therapy in children with Hodgkin's disease has ushered in a new wave of studies based on clinical staging only that are risk-adapted and that separate the patients with early-stage, favorable disease from those with advanced and unfavorable disease. The Stanford/Dana Farber/St. Jude collaborators began an early-stage, favorable protocol for children with clinical Stage I–II nonbulky disease using four cycles of VAMP and 15–25.5-Gy involved-field radiation. The reports of this study revealed freedom-from-relapse data in excess of 90% and were noteworthy because of the lack of toxicity and the excellent quality of life using this approach (36). Patients with advanced-stage and less favorable bulky Stage II, Stage III, and Stage IV disease received six cycles of VAMP/COP and 15–25.5-Gy involved-field radiation. The results have continued to show high overall survival, but the preliminary failure-free survival have not been as high as hoped. The final analyses are under way and will be reported separately.

The definitions of risk groups vary from study to study, as the prognostic indicators change. The Stanford/Dana Farber/St. Jude investigators refined their risk-adapted protocols to use three risk groups: favorable, intermediate, and unfavorable. The eligibility for the favorable risk groups requires clinical Stage I–IIA disease with a mediastinal mass ratio of $<1/3$ and <3 nodal regions of involvement. Intermediate risk includes Stage I–IIA disease with a mediastinal mass ratio $\geq 1/3$, extranodal "E" lesions, ≥ 3 involved nodal regions, and/or Stage IIIA disease. High risk is reserved for those with Stage IIB, IIIB, or IV disease. These studies are currently under way. The American, German-Austrian, and European cooperative groups have used slightly different definitions of risk groups, thus making comparisons across studies difficult.

This ongoing progress in pediatric Hodgkin's disease has brought forth a 19% increase in the cure rate from 1969 to the present (Fig. 2). Surveillance, Epidemiology, and End Results Program data now report a 94% 5-year relative survival rate in Hodgkin's disease for American children, ≤ 14 years old, the highest survival of all childhood cancers (37).

LEARNING IN THE FUTURE

Considering the extraordinary progress made during the past 30 years in pediatric Hodgkin's disease, one might question how it could be possible to build on this momentum and cure more children with even less toxicity. Several areas, however, hold promise for future advances.

Pathology and biology studies

The old Rye pathology classification has now been replaced by a new World Health Organization classification (38) that recognizes Hodgkin's disease as a lymphoma and separates nodular-lymphocyte predominant Hodgkin's dis-

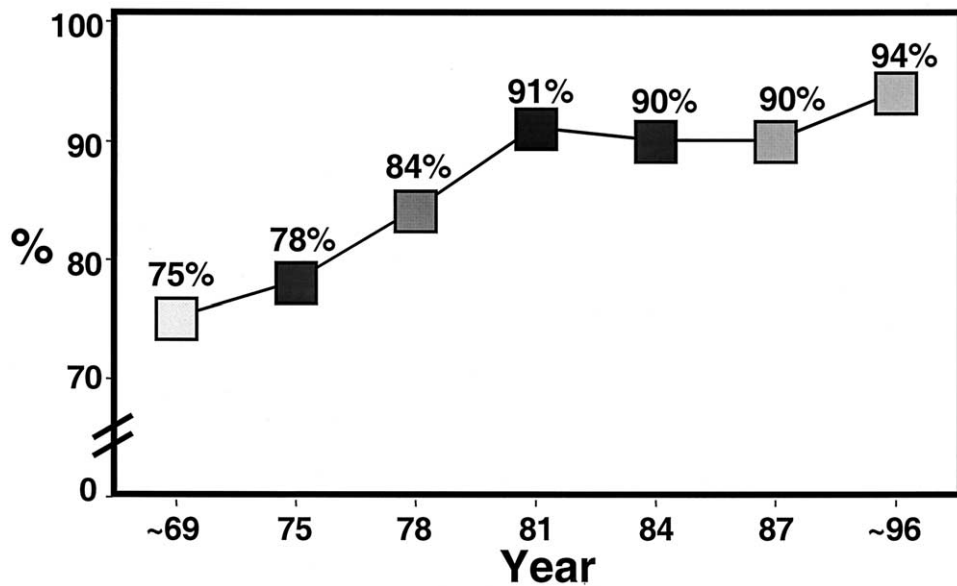


Fig. 2. Pediatric Hodgkin's disease, Surveillance, Epidemiology, and End Results Program 5-year relative survival data. Modified from Greenlee *et al.* (37), with permission.

ease from classic Hodgkin's disease. The older form of Hodgkin's disease previously thought to be lymphocyte predominant is now designated lymphocyte-rich, nodular or diffuse, within the category of classic Hodgkin's disease; the other categories of nodular sclerosis, mixed cellularity, and lymphocyte depletion remain unchanged.

Immunophenotyping studies are important in making the diagnosis and are now considered the standard of care (Table 1) (39). CD45 may be the most useful marker in the immunodiagnosis of Hodgkin's disease, because it is a negative marker, expressed in only 7% of classic Hodgkin's disease cases, but positive in a high proportion of B- and T-cell lymphomas. The CD15 and CD30 cluster of antibodies is present in 87–89% of classic Hodgkin's disease. The CD20 cluster detects mature B-cell antigens, such as seen in B-cell lymphoma and nodular-lymphocyte predominant Hodgkin's disease. Additional markers, such as antibodies against Epstein-Barr virus, latent membrane protein, CD40, CD3, epithelial membrane antigen, and other B- and T-cell markers, may also be helpful. Both morphologic and biologic criteria must be used to distinguish classic Hodgkin's disease from anaplastic large cell and peripheral T-cell lymphoma. Furthermore, classic Hodgkin's disease must be

differentiated from both low-grade and large B-cell lymphoma, as well as from T-cell-rich B-cell lymphoma and nodular-lymphocyte predominant Hodgkin's disease. Current management today dictates differing treatment for children with Hodgkin's disease and those with non-Hodgkin's lymphoma and other diseases with which Hodgkin's disease may be confused.

Staging

More accurate and less invasive staging techniques are commonly used in the treatment of children. Bulky nodal disease and the number of involved sites have been shown to be important prognostic factors (40). When using combined-modality therapy, staging laparotomy is seldom needed. In addition, although the lymphogram has been shown to have greater sensitivity than CT for evaluating retroperitoneal lymph nodes (41), the lymphogram is an invasive test that requires special expertise to perform and interpret and is routinely used only in a few pediatric centers today. CT of the chest, abdomen, and pelvis is now considered routine. ^{67}Ga is useful in the evaluation of supradiaphragmatic Hodgkin's disease, particularly in terms of assessing residual disease after therapy (42). Positron-

Table 1. Immunophenotyping studies in lymphoma

	CD45 (%)	CD15 (%)	CD30 (%)	CD20 (%)
Classic Hodgkin's disease	7	87	89	24
Nodular lymphocyte-predominant Hodgkin's disease	65	37	38	92
B-cell lymphoma	97	4	18	94
T-cell lymphoma	89	21	42	0

Modified from Weiss *et al.* (39), with permission.

emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) is currently under investigation as a diagnostic and monitoring tool for Hodgkin's disease. FDG-PET has been studied most commonly in adults, and the studies evaluating the role of FDG imaging have included both Hodgkin's disease and non-Hodgkin's lymphoma together (43, 44). In most series, FDG-PET has been shown to be superior in both sensitivity and specificity to conventional imaging by CT scanning, sometimes supplemented with gallium and MRI (45, 46). Persistent accumulation of FDG in a residual mass after treatment for lymphoma correlates with an 80–95% incidence of relapse or local recurrence (47, 48). In difficult cases in which residual masses persist after treatment, FDG-PET can separate patients who fall into a bad prognostic group, with residual active disease and a high incidence of relapse, from those in a good prognostic group, with a negative FDG scan and a much lower risk of recurrence. However, as many as 20% of adults treated for lymphoma who have residual masses and negative FDG scans eventually have a relapse (48, 49). Although, to date, no studies of FDG-PET have been done exclusively in children with Hodgkin's disease, we can look to the future, when FDG-PET will be used and studied systematically in the staging of children with Hodgkin's disease.

Defining risk groups

The challenge in refining therapy is to define precise risk groups to be able to prescribe appropriate risk-adapted therapy. A major goal today is to identify the disease characteristics associated with inferior EFS to intensify the treatment for patients with aggressive disease and to minimize the treatment and toxicity for the others. In a retrospective review, Smith *et al.* (50) analyzed 320 consecutive children and adolescents with Hodgkin's disease treated on combined-modality protocols during a 10-year period, with a median follow-up of 4.4 years. Factors prognostic for disease-free and overall survival were identified and a prognostic index developed on the basis of the following prognostic factors: age, gender, stage, histologic features, presence of B symptoms, erythrocyte sedimentation rate, initial white blood cell and hemoglobin levels, presence of bulky disease, and/or extranodal lesions (50). Factors associated with a consistently poor 5-year disease-free survival rate ranging from 69% to 79% were Stage IV, histologic features of nodular sclerosing Hodgkin's disease, B symptoms, elevated erythrocyte sedimentation rate, elevated white blood count, low hemoglobin, bulky mediastinal disease, and presence of extranodal disease. In multivariate analysis, male gender, advanced Stage IIB, IIIB, or IV disease, elevated white blood count, and low hemoglobin were associated with an elevated relative risk and poor disease-free survival. The presence of three or more of these prognostic factors was associated with a 5-year disease-free survival and overall survival rate of 63% and 77%, respectively. However, if the patient has none or only one of these factors, a 5-year disease-free survival and overall survival rate of 94% and 96%, respectively, can be expected. Two

factors yielded an intermediate-risk group with a 5-year disease-free and overall survival rate of 71% and 95%, respectively. This prognostic index may be useful in dividing patients into even more refined risk groups for subsequent studies to better tailor therapy and improve outcome for unfavorable risk children, and lessen the toxicity for the others.

Bone marrow and stem cell transplantation in Hodgkin's disease

The successful definition of risk groups can help define children who are candidates for bone marrow and stem cell transplantation. Currently, autologous peripheral stem cell and bone marrow transplantation is used for children who have a relapse after initial combined-modality therapy, those with multiple relapses, and those with an inadequate response to initial therapy. Several studies have shown survival rates ranging from 30% to 65% in children with relapsed Hodgkin's disease treated with myeloablative therapy followed by hematopoietic stem cell transplantation (51–53).

However, pulmonary toxicity, manifesting as nonbacterial, nonfungal, interstitial pneumonia, occurs in approximately 15% and diffuse alveolar hemorrhage occurs in 20% of children who undergo high-dose therapy; transplant-associated mortality occurs in approximately 10% (51, 53, 54). Although the diffuse pulmonary toxicity after myeloablative therapy and stem cell transplantation has been ascribed to thoracic irradiation or chemotherapy with bleomycin, bischloroethylnitrosourea (carmustine), or cyclohexylchloroethylnitrosourea (lomustine), Frankovich *et al.* (53) have demonstrated that a history of atopy (allergic rhinitis or asthma) is a significant predictor of subsequent pulmonary toxicity, manifesting as acute alveolitis, diffuse alveolar hemorrhage, acute respiratory distress syndrome, delayed interstitial pneumonitis, or bronchiolitis obliterans. These authors also reported a 44% incidence (15 of 34 patients) of idiopathic diffuse pulmonary toxicity after autologous transplantation among children, with an 80% incidence among those with an atopic history compared with 20% among those without an atopic history (Fig. 3). They noted that Reed-Sternberg cells of Hodgkin's disease produce interleukin (IL-13 and IL-5), which is important in the trafficking of inflammatory cells to the lung in Hodgkin's disease and believed that children with an atopic history have increased susceptibility to the development of inflammatory lung disease. This theory suggests that the absence of a history of atopy may be important in the selection of pediatric patients with Hodgkin's disease who are candidates for myeloablative therapy and stem cell/bone marrow reconstitution (53).

Novel therapies

Hodgkin's disease is responsive to many agents, making new drugs, immunotherapies, vaccines, and monoclonal antibodies all possible novel therapies. One interesting new agent for select patients with Hodgkin's disease is the

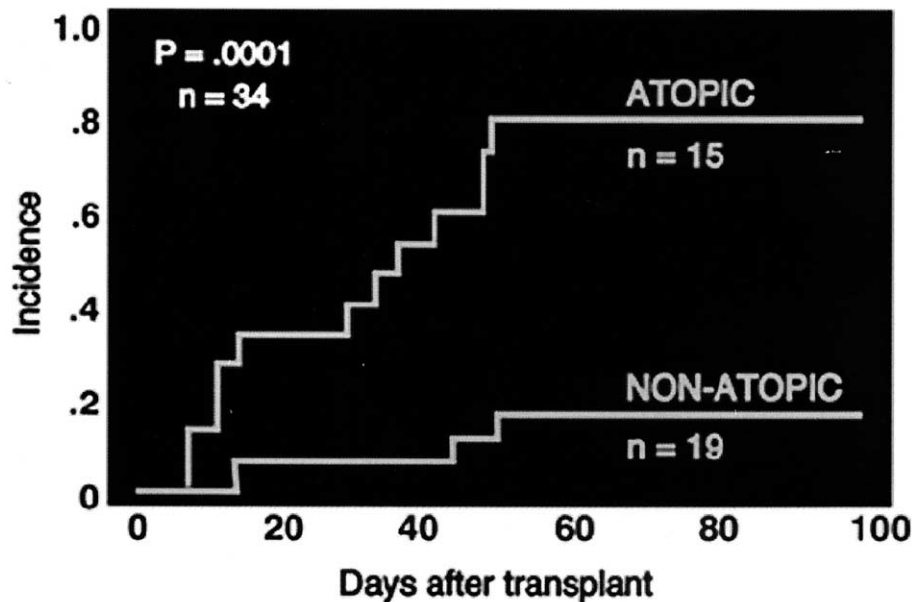


Fig. 3. Incidence of idiopathic diffuse pulmonary toxicity after myeloablative therapy and autologous hematopoietic stem cell transplantation among 34 children with relapsed Hodgkin's disease. Those with a prior history of atopy had an 80% incidence of pulmonary toxicity; the incidence was 20% for those without a history of atopy. Modified from Frankovich *et al.* (53), with permission.

anti-CD20 antibody, rituximab. Approximately 10–15% of pediatric Hodgkin's disease patients have the lymphocyte predominant Hodgkin's disease subtype, with CD20+ malignant cells. The collaborative experience of 37 children with lymphocyte predominant Hodgkin's disease histologic features from Stanford, Dana Farber, and St. Jude revealed a 10-year overall survival rate of 100% and freedom-from-relapse rate of 97% using standard therapy (Fig. 4). Because these children have an excellent outcome and because current therapy may carry risks of

long-term toxicity, a new agent with few adverse effects could hold additional promise for them. A Phase II trial using rituximab in 21 adults (19 assessable for response), with median follow-up of 12 months, revealed that all patients responded to treatment, with similar response rates among untreated and previously treated patients (55). The median time to progression was 10 months, and retreatment was also effective. No Grade III or IV toxicity occurred. These preliminary data suggest that rituximab is active and that a clinical trial testing efficacy and

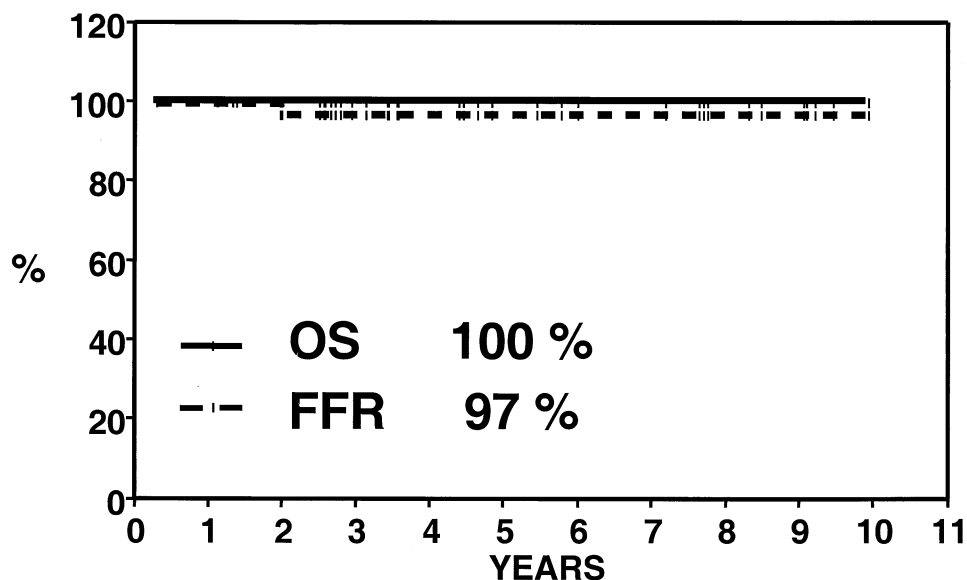


Fig. 4. Actuarial overall survival (OS) and freedom from relapse (FFR) rates among 37 children with lymphocyte-predominant Hodgkin's disease.

toxicity should be undertaken in children with CD20+ lymphocyte-predominant Hodgkin's disease. Thus, this agent, or another novel therapy, may take another subgroup of patients closer to our ultimate goal of cure without toxicity for children with Hodgkin's disease.

Juan A. del Regato recognized the challenges associated

with the treatment of children with Hodgkin's disease. He questioned cure; he questioned treatment without late effects. He posed the scientific inquiries that frame the treatment in children today and that have brought about cure to so many. We are indebted to this influential clinician, educator, and leader.

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