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Perspective

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The Impact of Drug Shortages on Children with Cancer — The Example of Mechlorethamine

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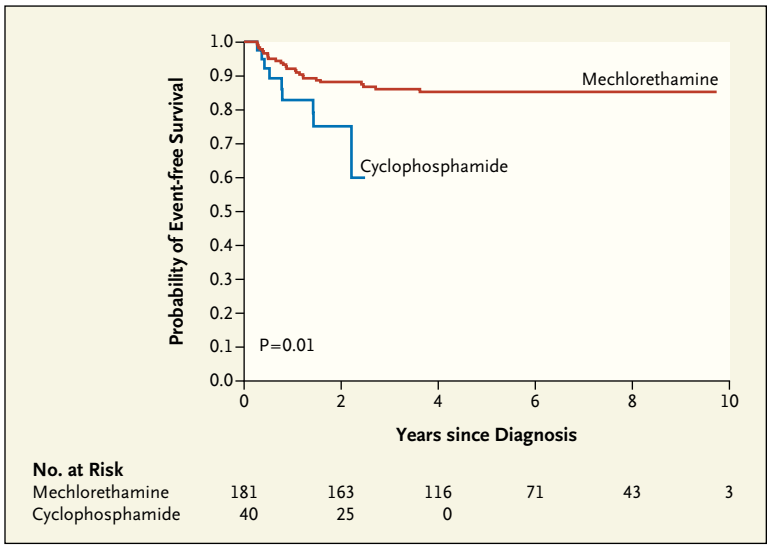
Over the past several years, patients and caregivers have faced an increasing number of drug shortages, predominantly of generic injectable agents. The reasons for these shortages are complex. Narrow profit margins for generic drugs have limited the incentive to produce them. Other reasons include the limited number of manufacturers, increased worldwide demand, shortages of raw materials, production problems, aging production plants, stockpiling, and long timelines for approval.[1] Patient care may suffer significantly as a result: alternative drugs must be prescribed, but the replacement may be less efficacious, more toxic, prohibitively expensive, or all of the above, and safety may be compromised if providers are unfamiliar with administering the substitute.

Shortages of anticancer agents are even more critical, because there may be no equivalents for the drugs that are in short supply, and conversion factors and dose adjustments may be unknown. Recent media coverage has highlighted shortages of cytarabine, daunorubicin, and methotrexate, which are essential for treating childhood leukemia, a highly curable cancer. Fortunately, those shortages were quickly resolved, and alternative strategies such as prioritizing patients for access to certain drugs and using equivalent agents sufficed to bridge the gap.

One shortage that hasn't made the news is that of mechlorethamine, or nitrogen mustard, one of the first anticancer agents, which was used in the 1960s in combination with vincristine, procarbazine, and prednisone in the MOPP regimen for Hodgkin's lymphoma. Although this regimen was effective, it was associated with secondary leukemia and infertility. Alternative chemotherapy combinations were developed to avoid these complications. In an effort to maintain excellent outcomes while minimizing toxicity, a 12-week chemotherapy regimen was developed at Stanford University (the Stanford V regimen) that included vinblastine, mechlorethamine, doxorubicin, vincristine, bleomycin, etoposide, and prednisone. This regimen's main features are an abbreviated course of treatment, unchanged or increased dose intensity of individual drugs, lower cumulative doses of bleomycin and doxorubicin than in other standard regimens, exposure to lower cumulative mechlorethamine than in MOPP, and omission of procarba-



Event-Free Survival Distributions among Children with Hodgkin's Lymphoma Treated with the Original Stanford V Regimen with Mechlorethamine, as Compared with Those Treated with a Modified Stanford V Regimen with Cyclophosphamide.

Two-year event-free survival was 75% among patients who received cyclophosphamide (SE, 12.5%) and 88% among those who received mechlorethamine (SE, 2.5%; P=0.01).

zine. This regimen proved to be effective while allowing for preserved fertility and reduced risk of secondary leukemia as compared with MOPP, and reduced risk of cardiopulmonary dysfunction as compared with other regimens in use.

The Pediatric Hodgkin Lymphoma Consortium, which includes St. Jude Children's Research Hospital, Stanford University, Dana–Farber Cancer Institute/Boston Children's Hospital, Massachusetts General Hospital, and Maine Medical Center, has conducted clinical trials for pediatric Hodgkin's lymphoma since the 1990s. It adopted the Stanford V regimen, along with response-based, low-dose radiotherapy, in 2002 for patients with high-risk Hodgkin's lymphoma and in 2006 for patients with intermediate-risk Hodgkin's lymphoma. More than 170 patients had been treated with this regimen in our studies when a shortage of mechlorethamine emerged in 2009. A review of the literature suggested that cyclophosphamide at a dose of 650 mg per square meter of body-surface area could safely be substituted for mechlorethamine 6 mg per square meter. When mechlorethamine became unavailable, we amended our studies to use cyclophosphamide instead. Although the COPP regimen (cyclophosphamide 600 to 650 mg per square meter, vincristine, procarbazine, and prednisone) has been widely used in adult and pediatric trials and was believed to be equivalent in efficacy to MOPP, no randomized study had ever compared the two.

Many published reports describe in detail the sources of drug shortages, as well as reactions of the Food and Drug Administration, the American Society of Clinical Oncology, or Congress. Other reports speculate on possible solutions, but few comment on individual patient safety.[2,3] Although concerns have been raised about reduced efficacy and possible adverse outcomes related to shortages of anticancer agents, we have seen no report documenting the adverse effects of these shortages on a specific patient population or the way in which a substitution has affected outcomes.

To assess the impact of the substitution that we were forced to adopt, we compared the probability of event-free survival among 181 patients who were treated with the original Stanford V regimen including mechlorethamine with the probability among 40 patients treated with the modified Stanford V regimen including cyclophosphamide. In this retrospective comparison, we discovered that treatment with cyclophosphamide was significantly less effective (2-year event-free survival, 75% with cyclophosphamide [SE, 12.5%] vs. 88% with mechlorethamine [SE, 2.5%; P=0.01 by the log-rank test]) (see graph). We can think of no credible explanation for this dramatic difference in event-free survival other than the drug substitution, since careful analysis of our data demonstrated that patients in the cyclophosphamide cohort did not have more unfavorable clinical features than those in the mechlorethamine cohort. In fact, patients in the cyclophosphamide cohort were less likely to have B symptoms (fever, unintentional weight loss, and night sweats) and more likely to have intermediate-risk or high-risk Hodgkin's lymphoma, with no difference in mediastinal bulk or stage distribution.

Follow-up is still short (median follow-up, 1.5 years in the cyclophosphamide group and 4.7 years in the mechlorethamine group), and no patient in the study has died, so there is no survival difference between the cohorts. However, patients who had a relapse received salvage therapy including intensive cytoreduction followed by autologous stem-cell

transplantation — therapy that is associated with infertility and a greater risk of long-term toxic effects. These complications might have been avoided if such patients had been treated with mechlorethamine. Moreover, it is unknown as yet whether salvage therapy has been successful in all patients who have had a relapse.

Almost 80% of children and adolescents with cancer can be cured with current therapy. Most of the curative treatment regimens are based on chemotherapeutic agents that have been available for decades, but some of these have recently been in short supply. These shortages are likely to have devastating effects on patients with cancer and must be prevented. For many of these agents, no adequate substitute drugs are available. Our results suggest that even promising substitute regimens should be examined carefully before adoption; what might appear to be a suitable alternative regimen may result in an inferior outcome — an intolerable situation for young people with curable diseases.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Withdrawal of Generic Budeprion for Nonbioequivalence

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The Food and Drug Administration (FDA) has completed a head-to-head bioequivalence study of single doses of the generic drug Budeprion XL 300 mg (extended-release bupropion hydrochloride, manufactured by Impax Laboratories and distributed by Teva Pharmaceuticals) and the brand-name drug Wellbutrin XL 300 mg (Biovail). The agency has concluded that Budeprion XL 300 mg cannot be considered therapeutically equivalent to the brand-name product. We at the FDA are therefore changing our bioequivalence recommendations for extended-release bupropion products and have asked other manufacturers of 300-mg extended-release bupropion products to conduct additional bioequivalence studies.

Within a year after gaining approval at the end of 2006, Budeprion XL 300 mg became the subject of intense media coverage describing adverse events in patients being treated for major depressive disorder who had switched to the generic drug from Wellbutrin XL. Approval of Budeprion XL 300 mg was based on the results of a bioequivalence study of Budeprion XL 150 mg and Wellbutrin XL 150 mg, which were extrapolated to the 300-mg product. Our new data provide direct comparative pharmacokinetic analyses of the 300-mg products.

According to current guidance from the FDA Center for Drug Evaluation and Research, conclusions that two drug products are bioequivalent should reflect significant agreement in pharmacokinetic parameters such that the entire 90% confidence interval associated with the generic-to-reference ratio of geometric means should fall within the bioequivalence limits of 80 to 125%.[1] Budeprion XL 300 mg did not meet these criteria in our bioequivalence study, which involved 24 healthy fasting volunteers and used a single-dose crossover design (see graph). The extent of bupropion absorption after the administration of the generic product, as reflected in the area under the curve of the plasma concentrations plotted over time, was 86% of the absorption with the brand-name product (see graph), but the corresponding 90% confidence interval was 77 to 96%. In addition, the mean peak plasma concentration (C_{max}) observed after the administration of Budeprion XL 300 mg was only 75% of that observed after the administration of Wellbutrin XL 300 mg (90% confidence interval, 65 to 87). In certain study participants, the C_{max} and the area under the plasma-concentration curve for Budeprion XL were less than 40% of the values with Wellbutrin XL. The C_{max} values for hydroxybupropion, the major active metabolite of bupropion hydrochloride, also failed to meet the FDA bioequivalence criteria.

The other major difference observed between Budeprion XL