Trends in the Treatment of Early-Stage Hodgkin Lymphoma

Researchers found that treatment selection for patients with early-stage Hodgkin lymphoma (HL) was influenced by socioeconomic factors and that guideline nonadherence may affect survival (J Clin Oncol. 2015;33:625-633). The treatment of patients with early-stage HL with combined modality therapy (CMT) (sequential chemotherapy and radiotherapy [RT]) became standard in the early 2000s, and until 2007 was recommended in the National Comprehensive Cancer Network guidelines for all such patients. Since 2007, an option for chemotherapy alone has existed.

Identifying groups that do not need RT to achieve a cure is an important area of research. Trials have had mixed results and there is uncertainty among oncology providers with regard to who can be safely spared RT. The authors of the current study set out to find factors that affected choice of treatment and how this impacted survival.

Adam Olszewski, MD, assistant professor at the Alpert Medical School of Brown University in Providence, Rhode Island, and colleagues conducted a retrospective study using the National Cancer Data Base. This database includes cancer registry records from more than 1500 accredited hospitals, and captures approximately 70% of all incident cancer cases in the United States. Variables collected include patient demographics, comorbidities, area socioeconomic status, tumor histology, stage of disease, and first course of therapy. Survival outcomes are reported only after 5 years of follow-up. The National Cancer Data Base provided records of 52,394 patients diagnosed with HL between 2003 and 2011, with survival data available for the group of patients diagnosed between 2003 and 2006. Of these, researchers identified 20,600 patients with early-stage HL who were treated with CMT or chemotherapy alone between 2003 and 2011. The majority had stage IIA nodular sclerosing HL.

The percentage of patients receiving CMT declined from 59% in 2003 to 45% in 2011, with an annual percent change of −3.1%. This decrease was most dramatic in women aged younger than 30 years, with the trends for women aged older than 50 years and men aged older than 70 years not found to be significantly changed. Treatment selection was associated with clinical and socioeconomic factors. CMT was used less often in patients with B symptoms, tumors occurring below the diaphragm, or disease of lymphocyte-depleted histology. Race was found to be a significant factor: black patients were less likely to receive CMT, even after adjustment for insurance, income, and education. Among all patients, those with private insurance had significantly higher odds of receiving CMT compared with those without insurance or those with Medicaid or Medicare.

KEY POINTS
- Overall survival was superior with the use of combined modality therapy (CMT) versus chemotherapy alone in this registry-based trial of patients with early-stage Hodgkin lymphoma.
- Guideline adherence was lacking.
- Patients with private insurance were more likely to receive CMT than the uninsured and those with Medicaid or Medicare.
"It is striking that in half of the early-stage HL cases, patients or clinicians decided not to pursue CMT, even though it was endorsed by guidelines through 2006," says Dr. Olszewski. "This is most likely because of numerous reports emphasizing late toxicity of radiation, which were highly publicized and led to some strong opinion statements favoring chemotherapy alone. But radiation doses and techniques have evolved dramatically, and it is not clear how relevant the outdated estimates of secondary cancers and cardiovascular disease will be anymore."

The 5-year overall survival (OS) rate of the entire group was 89.6%, and the 5-year relative survival (RS) rate, defined as the ratio of observed survival to expected survival in the matched general population, was 94.3%. Unadjusted 5-year OS estimates were 94.7% after CMT and 83.7% after chemotherapy alone. The unadjusted RS estimates were 97.6% for CMT and 89.2% for chemotherapy alone.

In analyses that used the propensity score to balance confounders associated with selection of treatment or with survival, OS was found to be significantly better for patients treated with CMT compared with those receiving chemotherapy alone, with a hazard ratio of 0.61. The estimated 5-year OS rate was 94.6% for CMT and 90.9% for chemotherapy alone. In the adjusted model, the RS analysis also favored CMT over chemotherapy alone, with an estimated 5-year RS rate of 97.5% versus 94.1%, respectively.

"While the current study shows a survival benefit to CMT and there is other evidence that radiotherapy can improve progression-free survival, and some evidence of short-term overall survival benefit, there is also longer-term data that indicate with additional follow-up the overall survival benefits of radiation may be lost or even unfavorable," says John Leonard, MD, professor of medicine and associate dean for clinical research at Weill Cornell Medical College in New York City, who was not involved in this study. "There are many factors to consider in making treatment decisions which could not be captured in this registry-based study."

Implications

Therefore, on bivariate analyses, researchers found that the use of CMT is continuously falling and that race and insurance status are significantly associated with treatment selection. However, in multivariable models that also included insurance status, other socioeconomic factors were not found to be associated with excess mortality. Furthermore, the patients who received CMT from 2003 to 2006, following the guidelines at the time, had a significant survival advantage.

"Because HL affects primarily young adults, we mainly emphasized the effect of having no [private] insurance or state-sponsored Medicaid insurance," says Dr. Olszewski. "It remains to be seen whether the favorable impact of [the] Affordable Care Act on the disparity in utilization of various treatments will be realized."

Major limitations of the study stem from the fact it was a retrospective analysis using registry data. The quality of treatment responses and the possible effect of treatment response on subsequent therapy, specific chemotherapy regimens or their duration, and possible confounders not in the registry, such as tumor bulk, could not be assessed.

The authors state that the major points of the study are that socioeconomic factors may affect the selection of curative treatments in patients with HL and that abandoning CMT beyond circumstances recommended in guidelines may affect survival. Having said that, it still is not entirely clear exactly which patients can safely skip RT.

"It is clear that there is significant risk of overtreating a large number of HL patients with radiotherapy and likely chemotherapy as well," concludes Dr. Leonard. "On the other hand, some fraction of patients may benefit. The challenge is identifying which patients should receive 'augmented' treatment, and in which patients it can be omitted, sparing short- and long-term toxicity as well as expense. Given the availability of new drugs in HL, as well as [the] evolution of radiotherapy techniques, better predictive markers of outcome are especially needed."

"I hope that our demonstration that clinicians or patients do not seem satisfied and are not adherent to guidelines will give impetus to larger-scale clinical trials that can bring those advances to patients with early-stage HL," says Dr. Olszewski.

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