A Perspective on the Evolution of Management of Cancer- and Chemotherapy-Induced Anemia

To help mark the 10th volume of JNCCN, I was asked to comment on the evolution of anemia management for patients with cancer over the past decade. I joined the panel for the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer- and Chemotherapy-Induced Anemia during its early years and have chaired it since 2004. Major changes in the NCCN Guidelines on anemia over the years have focused on 2 topics: erythropoiesis-stimulating agent (ESA) safety and the increasing use of intravenous iron therapy to treat the functional iron deficiency of these patients.

The latter half of the past decade was a turbulent time for the management of anemia from cancer and chemotherapy. A review of the published versions of the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia from 2002 to 2012 reveals reasonably consistent recommendations from 2002 to 2006 (to view the most recent version of these guidelines, visit the NCCN Web site at NCCN.org). During those 5 years, 8 versions of the NCCN Guidelines were published on NCCN.org, with no more than 2 updates in any year. Over the next 5 to 6 years, however, significant controversy about ESA safety and restrictions on ESA use led to 12 Guidelines versions between 2007 and 2011. Figure 1 presents a timeline of significant events as chronicled by the NCCN Guidelines on anemia related to ESA safety and intravenous iron therapy.

The Quiet Years (2002–2006)

The first NCCN Guidelines on anemia were published in 2002. The algorithm of these early guidelines was only 5 pages long, and the discussion section was 8 pages. In 2002, the Guidelines recommended that a patient hemoglobin (Hb) value less than 11 g/dL should trigger an evaluation for anemia and that symptomatic patients should be treated either with an ESA or red cell transfusion. Epoetin alfa was the only ESA available, and oral iron supplementation was recommended for a ferritin value less than 100 ng/mL and transferrin saturation less than 20%. The NCCN Guidelines further recommended aiming for an Hb of about 12 g/dL. The Guidelines discussion focused on ESA efficacy in transfusion avoidance and possible benefits on quality
of life (QoL). There was little mention of ESA safety issues, but the discussion did mention pending studies investigating the role of intravenous iron in managing the anemia of cancer and chemotherapy.

The 2003 NCCN Guidelines were very similar; one change was the addition of a longer half-life ESA product, darbepoetin alfa, to the treatment options. Positive QoL data associated with ESA use continued to accumulate. The Guidelines mentioned studies underway to evaluate the effects of ESA therapy in cancer patient survival.

New aspects of the 2004 NCCN Guidelines on anemia included alternative treatment schedules for both epoetin alfa and darbepoetin alfa. The 2003 study by Henke et al.\(^1\) that reported shortened survival in patients with head and neck cancer treated with ESAs was discussed, and the panel concluded that additional studies were needed focusing on clinical outcomes of ESA-treated patients with cancer. The first Cochrane Database meta-analysis on ESA treatment outcomes was published in 2004\(^2\) and reported that ESAs reduced transfusion requirements; however, data on QoL and adverse events, including survival, were inconclusive.

The 2005 NCCN Guidelines on anemia were the first with a significant focus on ESA safety and on the emerging data supporting the use of intravenous iron to treat functional iron deficiency associated with cancer and chemotherapy. Regarding ESA safety, an article by Leyland-Jones\(^3\) showing decreased survival of patients with metastatic breast cancer treated with ESAs was discussed, and an algorithm page was added specifically summarizing ESA safety issues (thrombosis, pure red cell aplasia, patient survival). Regarding intravenous iron therapy, the 2004 article by Auerbach et al.\(^4\) was highlighted as potentially changing anemia practice management, and recommendations were made regarding administration of specific intravenous iron products.

The 2006 Guidelines were similar to those in 2005. The discussion section included mention of an update of the Cochrane Database meta-analysis\(^5\) and a potential thrombosis risk identified with ESA use, but there were no additional survival studies.


In contrast, 2007 was an eventful year for the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia, with 3 versions produced on NCCN.org, reflecting the rapid changes in ESA safety and recommendations and requirements occurring that year. An updated meta-analysis of ESA safety was published in 2006 and discussed in the 2007 NCCN Guidelines; this update confirmed previous concerns for thrombosis risk and noted a non–statistically significant trend toward worse survival in patients with cancer receiving ESAs.\(^6\) In November 2006, the FDA issued an alert regarding high-target Hb values associated with ESA use, and in 2007 the FDA issued 2 “black box warnings” on ESA safety, both in response to clinical trial data suggesting that ESAs shortened the survival of patients with cancer. The FDA recommended limiting ESA treatment to patients with cancer receiving chemotherapy. Also in 2007, the Centers for Medicare & Medicaid Services (CMS) published a National Coverage Decision restricting ESA reimbursement to specific Hb levels and treatment schedules.

In 2008, the FDA required additional labeling changes for ESA use in patients with cancer. The Hb target to initiate treatment was lowered to less than 10 g/dL, and patients being treated with chemotherapy with curative intent were excluded from ESA treatment. A retrospective study of patients with cancer receiving blood transfusions reported that red blood cell transfusions were associated with increased risk of both thrombosis and mortality.\(^7\) The 2008 NCCN Guidelines on anemia reflected this new information and also recommended that physicians discuss with patients the benefits and risks of both ESAs and red blood cell transfusions. A lower target Hb for treatment was also recommended (10 to < 12 g/dL).
The NCCN Guidelines discussed a second publication on the use of intravenous iron therapy to treat the anemia of cancer and chemotherapy, and the recommendations noted that “intravenous iron appears to have superior efficacy” over oral iron supplementation.

In 2009, the NCCN Guidelines continued to reflect changes in the regulatory, reimbursement, and clinical practice areas of anemia management. A third Cochrane Database meta-analysis update was published in 2009 and confirmed an increase in ESA-associated mortality when targeting Hb greater than 12 g/dL. The 2009 NCCN Guidelines presented a benefits-to-risk table to assist with patient counseling when discussing ESA use versus red blood cell transfusion. A summary of the FDA-mandated Risk Evaluation and Mitigation Strategies (REMS) program for physicians and patients prescribing or receiving ESA therapy was also discussed.

That year was the first in which oral iron supplementation was discouraged in the NCCN Guidelines (“oral iron supplementation is less effective”). A distinction between treating absolute versus functional iron deficiency was also noted. The ferritin threshold to initiate iron therapy was increased to less than 300 ng/mL, reflecting the numerous clinical trials reporting benefits of intravenous iron over oral iron therapy for treating the functional iron deficiency anemia of cancer and chemotherapy.

The 2010 NCCN Guidelines were notable for reemphasizing not using ESAs to treat the anemia of cancer (non–treatment related). Otherwise, the 2010 NCCN Guidelines were similar to the 2009 Guidelines regarding ESA safety. A study-level meta-analysis of ESA safety published by Glaspy et al. in 2010 identified only thrombosis as a significant safety issue. The authors did not find survival to be affected by ESA therapy in this study. Further, the ferritin threshold value for using intravenous iron was increased to 800 ng/mL or less, based on newly published data using intravenous iron in patients with cancer.

The 2011 NCCN Guidelines identified treatment recommendations for 4 categories of cancer patients with anemia: patients with cancer and chronic kidney disease, patients receiving myelosuppressive chemotherapy with curative intent, patients treated with palliative intent, and patients receiving myelosuppressive chemotherapy without an identifiable cause for anemia. The Guidelines also provided a discussion on indications for red blood cell transfusion in patients with cancer. The 800 ng/mL or less ferritin threshold value for starting intravenous iron therapy was maintained. And interest remains: data from NCCN.org indicate that the current NCCN Guidelines on anemia are viewed by more than 1300 Web site visitors every month.

The current 2012 NCCN Guidelines (developed in 2011) contain no substantial revisions from the previous year. Three pharmacovigilance studies that prospectively evaluated survival of patients with cancer who received ESA therapies given as recommended found no adverse effects on survival, but the panel recommendations on ESA use remain unchanged.

**Observations and Predictions**

Based on events since 2007, the NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia have become more detailed and restricted. The current version of the algorithm (version 2.2012) is 15 pages long (vs. 5 for the first version in 2002). The increased length and detail is due to 2 reasons: 1) concerns over ESA safety in patients with cancer and the procedures/restrictions required to treat these patients (and obtain reimbursement); and 2) the increasing interest in using intravenous iron to treat functional iron deficiency in these patients (and to potentially decrease the need to use ESAs in iron-repleted patients). Despite the recent reassuring pharmacovigilance trial data indicating that ESAs are safe when used as recommended, I am not certain that the complexity of using ESAs or restrictions on their use will diminish in the near future. Thus, the NCCN Guidelines on anemia will continue to be a valuable resource for clinicians managing the anemia of cancer and chemotherapy.
One consequence of the ESA story outlined here is the increasing difficulty hospitals experience in attempting to obtain reimbursement for ESA therapy. The numerous requirements for using ESA therapy (e.g., appropriate patient category, checking iron stores and vitamin levels, appropriate initiation and target hemoglobin levels) represent, if not done correctly, potential reasons for denying reimbursement of this expensive therapy. At Huntsman Cancer Institute at the University of Utah, this led to the development of a pharmacy-managed anemia clinic\textsuperscript{11} to ensure both optimal patient management and reimbursement. This clinic also manages the use of intravenous iron therapy to optimize clinical outcomes. Other institutions may find this approach useful in managing anemic patients with cancer.

We do not currently know how intravenous iron therapy should optimally be used (frequent small intravenous bolus infusion vs. total-dose infusion) or whether there are unknown adverse events associated with long-term intravenous iron therapy.\textsuperscript{12} It would be prudent to incorporate evaluation of long-term adverse events, including survival, in future trials of intravenous iron therapy for patients with cancer.

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References