Bernatsky, et al: Editorial

Malignancies and Cyclophosphamide Exposure in Wegener’s Granulomatosis

Wegener’s granulomatosis (WG) is characterized by necrotizing small-vessel vasculitis and granulomatous inflammation. Although it classically involves the upper and/or lower respiratory tracts (being the most common form of vasculitis to involve the lungs) as well as the kidneys, it can occur in virtually any organ. Standard therapy for remission induction conventionally involves high-dose corticosteroids along with oral cyclophosphamide (CYC, 1–2 mg/kg/day). The high relapse rate of WG means repeated and prolonged courses of CYC in some patients. Such a regimen, while efficacious, is fraught with risks, as Faurschou and colleagues highlight in this issue of The Journal. Their work in a large cohort of patients with WG demonstrates tremendously high cancer risk related to cumulative CYC therapy.

Early studies assessing malignancy risk in WG have largely focused on CYC-related bladder cancers. This is believed to be mediated by the toxic metabolite acrolein, which is excreted into the urine. Subsequent studies in WG have brought to light important increased risks (compared to the general population) for leukemia, lymphoma, and non-melanoma skin cancer, in addition to bladder cancer. These more recent reports are consistent with observations in other populations (specifically, rheumatoid arthritis, RA), where CYC exposure was also shown to be associated with an increased risk of cancer, notably non-melanoma skin and hematological malignancies. Although CYC has long been thought to drive the increased risk of all of these malignancies in WG, the hypothesis was somewhat difficult to establish because of the almost ubiquitous exposure of patients to this agent. Talar-Williams, et al have previously demonstrated that the risk for bladder cancer was associated with both dosage and duration of treatment with CYC. In the most recent assessment of cancer risk in WG, Faurschou and colleagues extend the previous study’s results by demonstrating very high risks of acute myeloid leukemia [AML; standardized incidence ratio (SIR) 59.0, 95% confidence interval 12–72] and bladder cancer (SIR 9.5, 95% CI 2.6–24) in patients treated with cumulative CYC doses > 36 grams. The risk of these malignancies was not shown to be increased for patients who never received CYC or for patients treated with cumulative doses ≤ 36 grams. It is important to note that these huge cumulative doses are related to the oral route of administration, which exposes the patient to up to 2 mg per kg of CYC a day. In contrast, cumulative doses are lower when CYC is given by intermittent pulse therapy. One limitation of the work by Faurschou, et al is that disease activity, which may potentially confound the association between cancer risk and medication exposure, was not controlled for.

The risk-to-benefit ratio of pulse therapy, as an alternative to oral CYC, has been evaluated in several studies in the past decade. In one study, patients with newly diagnosed systemic WG were enrolled in a prospective, randomized trial (n = 50) of intravenous versus oral CYC for induction therapy. CYC was given for at least 1 year and then tapered. This study showed not only that pulse therapy was as effective as oral treatment for initial remission, but also that there were fewer adverse events, including mortality. However, in the long term, relapses occurred more often in the pulse therapy group (59.2%) than the oral CYC group (13%) in another study (of similar sample size, design, and duration) on vasculitis associated with antineutrophil cytoplasmic antibody (ANCA) and renal involvement, the cumulative CYC dose was halved in the pulse treatment group compared to the daily oral therapy group, and patient remission, relapse rate, progression to renal failure, and mortality appeared similar, with less toxicity in the pulse therapy group. On the basis of such data, some have concluded that intravenous administration of CYC is more desirable than oral administration, in spite of the possibility of increased relapse rates with pulse therapy.

To those who consider pulse CYC as a more optimal alternative to oral therapy, the study by Faurschou and colleagues may seem less relevant. However, as indicated...
above, there is no definitive consensus as to the preferred route for CYC in systemic vasculitis, and there are advocates for the role of oral CYC in some settings, for example, after failure of a pulse intravenous therapy to control disease9.

In some ways, the study of Fauruschou, et al can be seen as a response to the uncertainty regarding the extent to which malignancy in WG is driven by medication exposures versus the disease itself. This exact dilemma has been debated in other rheumatic diseases, such as RA and systemic lupus erythematosus (SLE). In RA and SLE, emerging data support a role for both immune system overactivity and immunosuppressive drugs10-12.

The picture seems clearer in WG, especially since there is little rationale linking bladder cancer to autoimmune disease activity. Moreover, in the work by Fauruschou, et al, the type of hematological malignancy most increased was AML (a malignancy well known to be associated with alkylating agents). This is in contrast to the marked increase in non-Hodgkin’s lymphoma (NHL) seen in systemic autoimmune rheumatic diseases like RA, SLE, and Sjögren’s syndrome (although some increase in lymphoma may be apparent in WG as well6). It is noteworthy that the risk of NHL is most dramatically increased in Sjögren’s syndrome, which is a population rarely exposed to CYC. Together, this evidence suggests the hypothesis that, in systemic autoimmune conditions, NHL risk is more driven by immune dysregulation, and leukemia risk is driven by exposure to alkylating agents and possibly other agents. Although, as noted previously, the study by Fauruschou, et al did not control for disease activity, this factor could be driving some of the risk (likely of more potential importance for hematological malignancies than for bladder malignancies). Differentiation between the effects of disease activity and its treatment remains very difficult8,6,13. The issue remains unresolved even in recent attempts to delineate the effects of newer biologic response modifiers [e.g., anti-tumor necrosis factor (TNF) agents] on malignancy risk in RA. International collaborative efforts are in progress to more clearly differentiate the effect of lupus activity (versus its treatment) on malignancy risk in SLE11.

Given their cancer risk profile, patients exposed to CYC require lifelong monitoring for malignant sequelae. In their retrospective WG cohort from 1969 to 1994, Knight and colleagues noted that the detection of early-stage lesions was rare; over a third of bladder cancers observed were already invasive at the time of diagnosis4. Hopefully, clinicians today have an increased awareness of bladder (and other) cancers in this population, and early detection will improve.

It is recommended that all patients treated with CYC undergo urinalysis and urine cytology every 6–12 months, even after CYC therapy is discontinued3. Any hematuria, atypia, or dysplasia should be followed up with an ultrasound of the urinary tract and cystoscopic evaluation. CYC-induced cystitis puts patients at higher risk for later bladder cancers, and thus for individuals with a history of CYC-induced cystitis, routine cystoscopy monitoring (every 1–2 years) should be considered.

Regarding recognition of other cancers in WG, non-melanoma skin cancers are rarely fatal, but can cause disfigurement if not diagnosed in early stages. In populations at high risk for these lesions, some have suggested screening, such as annual skin examinations by the patient’s family doctor or specialist14. A less resource-intensive alternative is patient education and self-screening for skin cancers.

Hematological cancers have considerable impact on mortality, and prompt detection of these malignancies requires awareness on the part of the treating physician, so that any symptom or sign of a lymphoma or leukemia (e.g., fever, fatigue, weight loss, abnormal results on complete blood counts) is investigated appropriately.

Although not addressed in the study by Fauruschou, et al, immunosuppressive drugs, particularly CYC, also increase the risk of cervical dysplasia15. Monitoring for cervical cancer (with vaginal smear testing as per established guidelines16) is thus important in women exposed to immunosuppressive therapies, particularly CYC.

Overall, the data are very clear regarding a tremendously increased risk of malignancy in patients exposed to significant amounts of CYC. The results of the study by Fauruschou and colleagues emphasize the need to develop less toxic yet effective alternatives for disease control in severe WG. Methotrexate, azathioprine, and leflunomide have all been used as steroid-sparing agents in WG, albeit generally in limited disease and/or in maintenance, not induction, therapy17. The use of azathioprine (after remission induction with CYC) has been demonstrated to not increase the rate of relapse compared with continued CYC in one study18. In patients with early ANCA-positive vasculitis without major organ involvement, low-dose methotrexate has been used instead of CYC for induction treatment, with similar remission rates. Unfortunately, blockade of TNF-α with etanercept for the maintenance of remission in WG has been shown to be inefficacious19; indeed, it appeared to confer a higher risk of solid malignancies. There have been several reports, in the setting of resistant disease or intolerance to CYC, of successful treatment with rituximab, including a prospective open-label pilot trial of 10 patients with refractory disease20. Mycophenolate has also shown promise in maintenance therapy21.

In summary, there is a continuing need for effective alternatives to toxic agents such as CYC for treating WG and other serious systemic autoimmune rheumatic diseases. For patients who have been exposed to CYC, vigilance is required to enable prompt detection of malignancies (bladder, skin, hematological) for which these patients are most at risk.
REFERENCES