The evolving paradigm of cancer risk related to cyclophosphamide therapy in granulomatosis with polyangiitis

Can judicious use of cyclophosphamide reduce the risk of cancer?

This editorial refers to Prolonged risk of specific malignancies following cyclophosphamide therapy among patients with granulomatosis with polyangiitis, by Mikkel Faurschou et al., on pages 1345–1350.

Granulomatosis with polyangiitis (GPA) is a potentially life-threatening ANCA-associated vasculitis (AAV) that typically involves the respiratory tract and the kidney. The introduction of glucocorticoid and CYC therapy in the 1960s dramatically improved the prognosis of affected patients, with 78% surviving at 5 years compared with a 1-year mortality in ~80% of untreated patients [1].

No conventional immunosuppressants have emerged as valid alternatives to CYC for the induction treatment of AAV, except for MTX in early systemic disease. The introduction of biologics such as rituximab has offered an exciting perspective for AAV treatment; however, trials comparing rituximab and CYC as initial therapy for AAV demonstrated that the former is not superior in inducing remission and that its short-term toxicity is also not negligible [2]. Thus, CYC still remains a cornerstone of AAV therapy and is unlikely to become of historical interest only.

CYC has severe side effects, including bone marrow suppression, impaired fertility, haemorrhagic cystitis and increased susceptibility to infections and cancer. While some of these (e.g. leucopenia) usually occur early, others—particularly malignancies—are more frequent in the long term and their risk is related to the cumulative dose of CYC. This is particularly relevant for GPA patients, who are more prone to relapse than patients with other vasculitides and therefore require repeat treatment courses. Thus, several attempts have been made to minimize CYC exposure in AAV. In initial studies [1], CYC was used as both induction and maintenance treatment, which resulted in a considerable cumulative dose. The adoption of a staged approach based on an induction-of-remission phase (with high-dose glucocorticoids and CYC) followed by a maintenance period (where CYC is replaced by AZA or MTX) has reduced the cumulative amount of CYC. Subsequent studies have also demonstrated that CYC exposure can be reduced if a pulse i.v. regimen is used instead of daily oral administration. Finally, preventive measures such as the use of mesna are now recommended to limit the occurrence of haemorrhagic cystitis, which is associated with an increased risk of bladder cancer [3].

Changes in the way CYC is used in AAV have probably influenced its long-term cancer risk. To address this point, we searched PubMed without any date limits for full papers on CYC-related toxicity using the search terms ANCA-associated vasculitis, Wegener, treatment, cyclophosphamide, and cancer risk. Early studies covering observation periods that dated back to the 1970s and 1980s indicated that CYC-treated GPA patients had a 2.0- to 2.4-fold increase in overall cancer incidence as compared with control populations [1, 4]. Cancer-type-specific analyses showed a significant excess risk for bladder cancer, non-melanoma skin cancer (NMSC) [1, 4, 5], lymphoma and leukaemia [4]. More recent studies, reflecting treatment periods spanning the 1990s to 2000s, have provided more reassuring findings, showing standardized incidence ratios (SIRs) (i.e. observed number of cancers divided by the expected number) of 1.6–2.1 for all cancer types [6, 7]. These studies have also shown that lymphoma is no longer over-represented in the patient population [7]. Interestingly, in a recent work with 535 AAV patients enrolled in four trials conducted by the European Vasculitis Study Group, the SIR for non-NMSC dropped to 1.3 (95% CI 0.90, 1.80) and was not significantly increased; thus, the excess cancer risk observed in AAV was driven mainly by NMSC [6].

Cancer risk is also determined by other immunosuppressants, although their influence is difficult to assess because AAV is seldom treated with these agents alone. AZA used for >12 months was associated with a 3-fold increase in all-cancer incidence after 5 years of follow-up [5]. In a long-term follow-up study, cancer incidence in AAV patients treated with MTX for induction was comparable to that of patients who received pulse CYC [8]. Cancer risk attributable to MMF seems lower than with other agents, as demonstrated in renal transplantation; in a study comparing MMF with AZA in AAV, malignancies tended to be more frequent in the latter group [9].

In this issue of Rheumatology, Faurschou and colleagues [10] report the results of a registry-based study on the long-term cancer risk following conventional immunosuppressive therapy in GPA. The authors had previously shown a greater-than-expected occurrence of NMSC among CYC-exposed patients and an increased incidence of bladder cancer and myeloid leukaemia among patients treated with high cumulative CYC doses.
after a median follow-up of 6 years [7]. In the current article, they extend the follow-up of their cohort to assess the risk of late-occurring malignancies. Among 293 patients, 255 had received CYC. The median follow-up was 9.7 years. The authors made important observations: first, the overall cancer risk did not increase in patients exposed to cumulative CYC doses of <36 g, with the only type of malignancy occurring in excess being NMSC. Second, among those treated with a cumulative dose of ≥36 g, the overall cancer incidence increased, mainly due to an increased incidence of NMSC, bladder carcinoma and myeloid leukaemia. Third, in this (high-dose) group, the risk of NMSC remained high during the entire follow-up period (with cases still occurring ≥20 years after diagnosis), while that of myeloid leukaemia and bladder cancer, respectively, peaked during the 5- to 9-year and ≥10-year latency periods (Table 1). A dramatic risk of bladder carcinoma was observed ≥10 years after diagnosis in patients exposed to ≥36 g, with a SIR of 29.0 (95% CI 10, 63). The authors could not assess the risk attributable to immunosuppressants other than CYC. Moreover, the cut-off of 36 g, chosen arbitrarily, cannot be used in clinical practice as a threshold for identifying the excess risk of cancer. Nevertheless, the results of this study are informative and underline the need for prolonged monitoring of cancer in GPA patients. However, they also show that judicious use of CYC, for instance by limiting it to the remission-induction period, may carry a low cancer risk.

Future studies are needed to provide more accurate tools for predicting cancer risk in CYC-treated GPA patients. Understanding CYC pharmacokinetics may be important for capturing individual susceptibility to adverse events. CYC is an inactive prodrug that undergoes activation through phase I metabolism by cytochrome p450 enzymes and phase II-inactivation primarily through conjugation via glutathione S-transferases. Functional polymorphisms of these enzymes impact enzyme activity and metabolite levels, so pharmacogenetic studies may help predict CYC toxicity.

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**Table 1** Schematic representation of cancer risk with respect to cumulative CYC dose and follow-up duration

<table>
<thead>
<tr>
<th>Cumulative CYC dose</th>
<th>Low dose</th>
<th>High dose</th>
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<tr>
<td><strong>&lt;5 years</strong></td>
<td>↑ NMSC</td>
<td>↑ all cancer types ↑ NMSC</td>
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<tr>
<td><strong>5-10 years</strong></td>
<td>↑ NMSC</td>
<td>↑ bladder cancer ↑ NMSC</td>
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<tr>
<td><strong>&gt;10 years</strong></td>
<td>↑ NMSC</td>
<td>↑↑↑ bladder cancer</td>
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↑: moderate increase in risk; ↑↑: marked increase in risk; ↑↑↑: severe increase in risk; NMSC: non-melanoma skin cancer.

This table has been created by extrapolating data reported in references [4, 7, 8, 9]; low dose and high dose refer to a cumulative dose generally lower or ≥36 g, respectively.

