Cancer and Rheumatoid Arthritis

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KEYWORDS

• Cancer • Rheumatoid arthritis • Disease-modifying antirheumatic drugs
• Biologic therapy

KEY POINTS

- Patients with RA should undergo age- and sex-appropriate cancer screening. No additional screening is recommended for patients on DMARDs.
- Management of RA in patients with cancer requires a multidisciplinary approach that considers type of cancer, stage, prognosis, and life expectancy, and that takes into account patient values.
- Current evidence suggests that biologic and synthetic DMARDs can be used safely in patients with RA and a prior diagnosis of cancer with no evidence of disease for at least 5 years.
- There is a knowledge gap with respect to the effects of bDMARDs and tsDMARDs on cancer outcomes in patients with RA and active cancer.
- Patients with RA undergoing cancer therapy need to be carefully monitored because they are at increased risk of complications.

The link between cancer and rheumatoid arthritis (RA) is complex. With advances in the knowledge of the pathophysiology, long-term outcomes, and development of new agents for cancer and RA, the relationship between these diseases is becoming more evident, and also more challenging. Here we describe related clinically important issues: cancer risk in RA, cancer risk related to therapy to treat RA, treatment of RA in patients with cancer, and treating cancer in patients with RA.

RA is an inflammatory autoimmune condition that symmetrically affects the small joints of the hands and feet and eventually involves large joints. The global prevalence of RA is almost 20 million and the incidence and prevalence rates of RA are increasing.[1] If not treated RA progression results in damage of articular bone and

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cartilage. In the past two decades the development of several new agents has revolutionized the treatment of RA resulting in improved clinical outcomes.[2] However, there are uncertainties as to whether these newer agents used to treat RA can increase the risk of cancer or affect its progression. To determine this, it is essential to first understand the baseline risk of cancer in RA.

CANCER RISK IN RHEUMATOID ARTHRITIS

The association between cancer and RA was first reported in 1978 in a study that identified an increased risk of lymphoma in patients with RA.[3] Since then several observational studies have been conducted to evaluate the risk of cancer in patients with RA. A recent meta-analysis conducted by Simon and colleagues[4] included studies from 2008 to 2014, and in their analysis, they also included studies that were previously analyzed by Smitten and colleagues[5] from 1990 to 2007. The pooled results showed that the standardized incidence ratio (SIR) in patients with RA compared with the general population for any cancer (all sites) was 1.09 (95% confidence interval [CI], 1.06–1.13). However, the risk was not the same across all cancer sites.

In the meta-analysis by Simon and colleagues,[4] the overall pooled SIR for lymphoma was 2.46 (95% CI, 2.05–2.96) for malignant lymphoma, 3.21 (95% CI, 2.42–4.27) for Hodgkin disease, and 2.26 (95% CI, 1.82–2.81) for non-Hodgkin lymphoma. The risk of lung cancer (SIR 1.64; 95% CI, 1.51–1.79) and melanoma (SIR 1.23; 95% CI, 1.01–1.49) were also increased. In contrast, however, the risks of breast cancer and of colorectal cancer were decreased, with SIR of 0.86 (95% CI, 0.73–1.01) and 0.78 (95% CI, 0.71–0.86), respectively.

This differential risk of cancer across sites may be attributable to several reasons. First, it is well known that inflammation in general and inflammatory cells play a role in the development of neoplasms.[6] RA causes a chronic inflammatory state and thus, RA itself, by causing a persistent inflammatory status, could be responsible for the increased risk of lymphoma.[7–9] Sustained immune activation in patients with Sjögren syndrome and Hashimoto thyroiditis has been linked to mucosa-associated lymphoid tissue lymphomas.[10] Many other cancer types have also been associated with chronic inflammation,[6,11,12] providing further evidence that chronic inflammation may play a role in lymphoma development in patients with RA. Second, cancer and RA could have shared risk factors, as is seen with lung cancer and RA. Smoking is a risk factor for developing lung cancer in up to 85% of cases,[13] and is also a known risk factor for RA, increasing risk up to 40%.[14] Inflammation in the airways is common in RA, even at early stages, and it has been suggested that it triggers the production of pathogenic antibodies, especially against citrullinated antigens, causing RA.[15] In addition, patients with RA can develop interstitial lung disease over time. It has been suggested that preexisting interstitial lung disease is associated with lung cancer, because many patients present with parenchymal imaging findings at cancer diagnosis.[16,17] Again, it is unclear whether this represents the effects of a common risk factor, primarily smoking, or whether the inflammation and fibrogenetic pathways related to interstitial lung disease might result in carcinogenesis. This relationship has not been studied in patients with RA.

Patients with RA have a lower risk of colorectal cancer. The cyclooxygenase (COX)-2 enzyme pathway is responsible for prostaglandin E_2 production, a known regulator of key oncogenic processes.[18] It is known that selective COX-2 inhibition results in tumor regression,[19] and at a population level, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), which are COX inhibitors, is associated with a decreased risk of colorectal cancer.[20,21] NSAIDs are commonly used for pain control in patients with RA,

even before RA diagnosis, and perhaps a similar effect to that seen in the general population of reduced risk of colorectal cancer may be attributable to the common use of NSAIDs.

Patients with RA also have a decreased incidence of breast cancer.[22] The decreased risk is seen before and after patients develop RA. Because there is a female predominance for RA, it has been suggested that hormonal factors may play a role; however, women with breast cancer who have received antiestrogen therapy with tamoxifen or aromatase inhibitors do not seem to be at increased risk for RA compared with those who do not receive these therapies.[22]

Genetic predispositions and gene-environment interactions may also play a role in the differential risk of cancers in patients with RA, which needs further exploration.

CANCER RISK IN RHEUMATOID ARTHRITIS IN ASSOCIATION WITH USE OF ANTIRHEUMATIC DRUGS

The mainstay of RA treatment is disease-modifying antirheumatic drugs (DMARDs). These agents are categorized into conventional synthetic (cs) DMARDs, biologic (b) DMARDs, and targeted synthetic (ts) DMARDs. With the increasing use of DMARDs in the management of RA, there is a critical need to understand whether or not the risk of cancer is increased with these agents. Here we briefly describe the risk of de novo cancer specifically in patients with RA receiving csDMARDs, bDMARDs, and tsDMARDs.

Conventional Synthetic Disease-Modifying Antirheumatic Drugs

The most commonly used DMARDs in RA are csDMARDs and include methotrexate, sulfasalazine, hydroxychloroquine, cyclosporine, azathioprine, and leflunomide. These agents are used as single agent or in combination with other DMARDs. Methotrexate is considered to be a safe and effective therapy for RA.[23] Overall methotrexate does not seem to increase cancer risk at large.[24] However, an Australian study[25] showed an increased risk of melanoma, non-Hodgkin lymphoma, and lung cancer in patients with RA exposed to methotrexate. This study did not have a control group of untreated RA; hence, it is difficult to ascertain whether the increased risk was from methotrexate or from the disease itself, especially in an Australian population with a high baseline risk of melanoma. In Japanese patients with RA a higher dose of methotrexate was associated with an increased risk of lymphoproliferative diseases.[26] Conflicting results of cancer risk have also been reported with cyclosporine,[27–29] azathioprine,[30] and leflunomide use in RA.[31] Lastly, little evidence is available on the use of sulfasalazine and hydroxychloroquine and cancer risk; however, neither are thought to be significant immunosuppressants.

Biologic Disease-Modifying Antirheumatic Drugs

Since the late 1990s, bDMARDs have become the second commonest class of DMARDs used in RA management. They are broadly categorized into tumor necrosis factor-α inhibitors (TNFi) (etanercept, adalimumab, certolizumab pegol, golimumab, infliximab, and related biosimilars) and non-TNFi agents (tocilizumab, sarilumab, abatacept, anakinra, and rituximab). In patients with RA there is conflicting evidence if TNFi increases cancer risk. Some meta-analyses and registry data have shown no increased cancer risk in patients receiving TNFi,[32–35] but other studies have shown increased risk of nonmelanoma skin cancer.[36–38] Similarly conflicting results have been reported for lymphoma risk.[39,40] However, TNFi agents are used in patients with severe disease, and deciphering the effects of RA, which is associated with

increased baseline lymphoma risk, especially in those with persistently active disease, from the potential effects of treatment with TNFi is challenging.

The non-TNFi are used typically following inadequate response to other DMARDs and/or TNFi. A claims-based study of three large US insurance companies[41] and a Swedish study[42] did not show increased risk for cancer with tocilizumab, an interleukin-6 receptor inhibitor; abatacept, a fusion protein composed of the Fc region of the immunoglobulin IgG1 and the extracellular domain of cytotoxic T-lymphocyte-associated protein 4; or rituximab, a chimeric monoclonal antibody against CD20. However, nonmelanoma skin cancers were excluded in evaluation of the primary outcome in both studies. In the Swedish study, an increased risk of squamous cell skin cancer was observed in the abatacept cohort versus csDMARDs (hazard ratio [HR], 2.15; 95% CI, 1.31–3.52). However, because of the limitations of the study, authors concluded that firm conclusions could not be made. Less information is available for anakinra, an interleukin-1 receptor antagonist, rarely used for RA. One challenge in assessing the risk of non-TNFi is that most patients with RA receive TNFi before non-TNFi agents, so disentangling the effects of continued risk from TNFi from the potential confounding by indication is problematic.

Targeted Synthetic Disease-Modifying Antirheumatic Drugs

The agents available for the treatment of RA are expanding. Currently there are three tsDMARDs approved for RA treatment. Tofacitinib, baricitinib, and upadacitinib are all janus kinase inhibitors. These agents are small molecules and available in oral formation. No signals of cancer risk were observed with tofacitinib in a meta-analysis of 4000 patients from clinical trials,[43] and in 3-year data of postmarketing surveillance from Pfizer.[44] Limited other information is available on the cancer risk with tofacitinib and the other janus kinase inhibitors. As such the limited evidence thus far stems from clinical trials, and well-controlled large observational studies are needed to clarify cancer risk with tsDMARDs.

CANCER SCREENING IN PATIENTS WITH CANCER

In patients with RA and no prior cancer, the nationally recommended age- and sex-specific cancer screening guidelines for breast, cervical, endometrial, colorectal, lung, and prostate should be followed.[45] In a recent systematic review of guidelines, we found agreement in most guidelines to screen for cancer before RA therapy initiation, but disagreements on the comprehensiveness of screening were noted.[46] In the same review, there was an overall agreement to be vigilant for symptoms or signs of cancer among patients with RA receiving DMARDs, but specific details were lacking. The benefits of screening for skin cancer have not been thoroughly evaluated; however, this may be considered, especially in patients receiving bDMARDs because some studies have shown increased risk of nonmelanoma skin cancer.

SAFETY OF DISEASE-MODIFYING ANTIRHEUMATIC DRUGS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND PRIOR OR CONCOMITANT CANCER

In patients with a history of cancer or with active cancer, the use of DMARDs may confer a different risk profile as it relates to recurrences and development of a second new cancer. csDMARDs, including methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine, do not have significant immunosuppressive properties and are often used in patients with RA and cancer, which is not considered a contraindication for their use, although well-controlled data are scarce.[46,47] However, clinical trials of bDMARDs and tsDMARDs have systematically excluded patients with prior cancer

because of initial concerns of the possible adverse effects on tumor immunity. Hence, the available evidence arises from observational data, and recommendations are largely based on expert opinion. Most of these observational studies have evaluated bDMARDs, and no studies have evaluated tsDMARDs in patients with cancer.

We summarize the evidence from observational studies on the use of DMARDs in patients with RA and cancer in **Tables 1** and **2**. Four European registries have provided data: (1) the British Society for Rheumatology Biologics Register, a national prospective observational study established in the United Kingdom[48–51]; (2) the Swedish biologics register (Anti-Rheumatic Therapy in Sweden)[52–54]; (3) the nationwide Danish DANBIO Registry[55,56]; and (4) the nationwide German biologics register RABBIT.[9] In addition, three other studies have evaluated the effects of bDMARDs in patients with prior malignancy in the United States using the national Veterans' Affairs administrative databases and electronic medical records,[57] and the Medicare administrative database.[58,59]

Eleven studies evaluated new or recurrent cancer in patients with RA who received TNFi compared with those who received csDMARDs (see **Table 1**). Of these, six studies showed a numerical, but not statistically significant, increased risk of new or recurrent cancer.[9,52–54,56,58] One study using data from the Medicare registry showed increased risk of a second nonmelanoma skin cancer (adjusted HR, 1.49; 95% CI, 1.03–2.16) in patients with prior nonmelanoma skin cancer receiving TNFi.[59] Two studies evaluated TNFi in patients with cervical carcinoma in situ and none progressed to cancer.[50,55]

Three studies evaluated the effect of rituximab in patients with prior malignancy,[51,56,59] of which two showed a numerical but statistically nonsignificant increased risk of second malignancy (see **Table 2**).[56,59] One study evaluated the effects of anakinra (n = 11),[9] and another evaluated the effects of abatacept compared with methotrexate monotherapy on risk of second nonmelanoma skin cancer (HR, 1.40; 95% CI, 0.48–4.03)[59]; however, no firm conclusions could be drawn because of the limited sample sizes. Most studies did not show statistically significant differences among groups; however, clinically meaningful risk cannot be ruled out given the effect size of the estimates and that several of the 95% CIs had upper limits greater than 2.0. Furthermore, most studies analyzed data from European registries, had small sample sizes, evaluated TNFi alone, had primarily patients with a remote history of cancer, and were not able to account for all confounders, especially cancer site and/or stage. There is still an urgent need for data to evaluate (1) differential effects of bDMARDs by cancer stage, especially in patients with active cancer or in those with advanced stage at primary diagnosis; (2) potential differences according to cancer type and histology; (3) safety and cancer outcomes on patients receiving non-TNFi biologics or tsDMARDs; and (4) cumulative dose and time-varying effects of these agents on cancer outcomes.

RECOMMENDATIONS ON THE MANAGEMENT OF RHEUMATOID ARTHRITIS IN PATIENTS WITH CANCER

We recently summarized published recommendations on the use of DMARDs in patients with RA and cancer.[46] These guidelines were based primarily on expert opinion, given the lack of evidence for the use of specific RA therapies across various cancers, and differences were observed among recommendations. Guidelines evaluating development of de novo cancer in a patient with RA generally agreed that the treatment of RA should be re-evaluated and most recommended discontinuation of bDMARDs. For patients with preexisting cancer who develop RA, most

Table 1
Risk of recurrent or new primary cancer development in patients with RA and cancer receiving TNFi versus csDMARDs

Country (Registry)	Study	TNFi	csDMARDs	Measure	Point Estimate (95% CI) TNFi vs csDMARDs (Ref)	Prior Cancer	Outcome	Adjustment Factors
United Kingdom (BSRB)	Dixon et al,[48] 2010	177	117	IRR	0.45 (0.09–2.17)	Any cancer except CIS and NMSC	New primary, recurrence, metastases	Propensity adjusted
	Mercer et al,[49] 2012	177	106	HR	0.70 (0.26–1.94)	Skin cancer	BCC	Treatment weighting
	Mercer et al,[50] 2013	190	48	—	None in TNFi group	CIS	Female genital cancer	None
	Silva-Fernandez et al,[51] 2016	243	159	HR	0.56 (0.36–0.88)	Any cancer except NMSC	New or recurrent cancer except NMSC	Age, gender, and smoking status
Sweden (ARTIS)	Raaschou et al,[53] 2013	54	295	aHR	3.2 (0.80–13.1)	Invasive or in situ melanoma	New melanoma	Age and sex
	Raaschou et al,[52] 2015	120	120	aHR	1.10 (0.40–2.80)	Breast cancer	Recurrence	Breast cancer characteristics and comorbidities
	Raaschou et al,[54] 2018	467	2164	aHR	1.06 (0.73–1.54)	Solid organs	Recurrence	Sex, birth year, index cancer year of diagnosis, type and stage, education level, and comorbid conditions
Denmark (DANBIO)	Cordtz et al,[55] 2015	233	442	—	None in either group	CIS or CD	Progression	None
	Dreyer et al,[56] 2018	1326[a]		aHR	1.21 (0.73–2.03)	Any cancer except NMSC	Second malignancy	Age, gender, calendar time, cancer site, and extent of disease
				aHR	1.42 (0.91–2.20)		Death	

Germany (RABBIT)	Strangfeld et al,[9] 2010	72	43	IRR	1.40 (0.50–5.50)	Any cancer except NMSC	Recurrence	None
United States (Veterans Affairs)	Philips et al,[57] 2015	31	149	aHR	0.75 (0.31–1.85)	HNC	Recurrence or HNC-attributable death	Age, stage at diagnosis, years from RA to HNC diagnosis, modified Romano score, smoking, alcohol, radiation, chemotherapy, surgery
United States (Medicare)	Mamtani et al,[58] 2016	273	1092	HR	1.11 (0.64–1.95)	Breast cancer	Breast cancer	No covariates modified HR >10% hence not adjusted for
	Scott et al,[59] 2016[b]	109	335	aHR	1.49 (1.03–2.16)	NMSC	Second NMSC	Anti-TNF exposure before incident NMSC; no other covariates modified HR by >10%

Abbreviations: aHR, adjusted hazard ratio; BCC, basal cell carcinoma; CD, cervical dysplasia; CIS, carcinoma in situ; HNC, head and neck cancer; IRR, incidence rate ratio; NMSC, nonmelanoma skin cancer.

[a] Total patients with extent of disease recorded.

[b] Number of patients in each group unknown, number of events reported.

Data from Refs.[9,48–59]

Table 2
Risk of recurrent or new primary cancer development in patients with RA and cancer receiving rituximab versus csDMARDs

Country (Registry)	Study	RTX	csDMARDs	Adjusted HR (95% CI) RTX vs csDMARDs (Ref)	Prior Cancer	Outcome	Adjustment Factors
United Kingdom (BSRB)	Silva-Fernandez et al,[51] 2016	23	159	0.44 (0.11–1.82)	Any cancer except NMSC	New or recurrent cancer except NMSC	Age, gender, and smoking status
Denmark (DANBIO)	Dreyer et al,[56] 2018	1326[a]		1.05 (0.47–2.34) 1.11 (0.53–2.35)	Any cancer except NMSC	Second malignancy Death	Age, gender, calendar time, cancer site, and extent of disease
United States (Medicare)	Scott et al,[59] 2016	320[b]	—	1.44 (0.26–8.08)	NMSC	Second NMSC	RTX exposure before incident NMSC; no other covariates modified HR by >10%

Abbreviations: NMSC, nonmelanoma skin cancer; RTX, rituximab.
[a] Total patients with extent of disease recorded.
[b] RTX with methotrexate versus methotrexate. No of patients unknown; number of events are reported.
Data from Refs.[51,56,59]

recommendations suggested that bDMARDs should not be used in patients with active cancer and could be used primarily only in those with no evidence of disease. In general, use of csDMARDs was considered safe.

Several guidelines addressed their recommendations from the perspective of time from cancer diagnosis. For patients with a history of cancer of at least 5 years, most guidelines considered bDMARDs to be generally safe but recommended caution with use. Some guidelines did not recommend use of TNFi at all in patients with preexisting cancer. For patients with a more recent history of cancer, of 5 years or less, most guidelines did not recommend treatment with TNFi. With respect to other non-TNF bDMARDs, most stated that these agents could be used with caution. Abatacept was not recommended by some. In general, rituximab was considered to be safe. Consultation with an oncologist was recommended before initiation of any bDMARDs. No clear guidance was provided on treatment with tsDMARDS because many of these recommendations were published before the approval of these agents, but those who considered it, stated that csDMARDs therapy was preferred.

In patients with a history of a hematologic cancer, csDMARDs were preferred over TNFi, based on the American College of Rheumatology guidelines, but the Canadian guidelines expressed caution against the use of leflunomide and methotrexate in patients with a history of lymphoma. The consensus of most guidelines was that rituximab can be used, and abatacept and tocilizumab should be used with caution, but were nevertheless preferred over TNFi.

Some guidelines considered patients with premalignant conditions. Treatment with bDMARDs or cyclosporine was not recommended, or caution was advised if used. Among bDMARDs an exception was rituximab, which in one guideline was suggested to be a consideration in patients with in situ cancer.

Most guidelines considered cancer as a class, and distinctions were only provided in some with respect to solid tumors, hematologic cancers, or skin cancers. Although duration from diagnosis of cancer was often considered, other important issues, such as stage of disease, prognosis, potential for cure, or life expectancy, were not addressed. These are issues that are fundamental for decision-making and that need to be considered at the individual level, taking into account patient preferences and values for quality of life and survival. Given the uncertainties on the potential effects of bDMARDS and tsDMARDS on recurrence and survival in patients with recently diagnosed cancer, patients may have different preferences, as exemplified next:

- Patient A is a 62-year-old woman with RA and recently diagnosed with estrogen-positive stage 1 breast cancer. She elects to continue therapy with TNFi because the 10-year probability of survival for this cancer after surgery, radiation, and hormonal therapy is high.
- Patient B is a 35-year-old man with RA and stage 3 melanoma. The survival rates for this cancer are not as good as for Patient A. Furthermore, melanoma is a highly immunogenic tumor, susceptible to immune attack. The patient wants to minimize the risk of a potential recurrence after treatment and decides to stop TNFi therapy.
- Patient C is a 68-year-old woman with RA, well controlled with TNFi, just diagnosed with metastatic adenocarcinoma of the pancreas. Given the poor prognosis of her cancer, the patient decides to continue treatment with TNFi to maintain her symptom control and maximize her quality of life for the remaining time she may survive.

For these three patients with RA and recently diagnosed cancer, there is no distinction in the recommendations about treatment with TNFi according to published

guidelines. However, their age, type of cancer, stage, and prognosis, and patient values, are instrumental in informing the most appropriate therapeutic decision.

USE OF CORTICOSTEROIDS IN PATIENTS WITH RHEUMATOID ARTHRITIS AND CANCER

Corticosteroids are frequently used in patients with cancer and RA to treat flares or as bridge therapy before other DMARDs can be started. These drugs are also used in the treatment of certain cancers, such as lymphoma or myeloma, and in addition, they play an important role in supportive therapy.[60] Dexamethasone is often used concomitantly with chemotherapy infusions to reduce nausea and vomiting. For patients with advanced cancer, corticosteroids are often used to improve performance status, and in this situation, dosing is higher.

The effects of chronic steroid therapy on cancer recurrence or progression are largely unknown. Because corticosteroids are potent, wide-ranging, immunosuppressant drugs, they could conceivably impair tumor immunity. However, this issue remains controversial because some studies report tumor progression and others inhibition.[61] These effects may vary according to tumor type because corticosteroids are effective in the treatment of lymphoproliferative diseases. With the advent of immunotherapy, there is also limited evidence that suggests that patients with cancer who are treated with corticosteroids at a dose of greater than or equal to 10 mg prednisone equivalent at the initiation of immunotherapy may have worse cancer outcomes than those who do not.[62] Given this knowledge gap with respect to cancer outcomes, for patients requiring corticosteroids only for management of RA flares, and not as treatment of their cancer, low doses are recommended. High dosages can also increase the risk for infection, a common complication in the cancer population.

CANCER TREATMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS

The treatment of cancer is often considered a priority compared with comorbidities, such as RA; hence, it is common that RA treatment is discontinued or withheld for a period of time. The consequences of such gaps in RA treatment on patients' outcomes and quality of life are unknown and have not been clearly documented.

Surgery

Surgery is one of the pillars of cancer therapy. Management of patients with RA in the perioperative setting can present unique challenges. Patients with RA frequently use NSAIDs, which inhibit COX-1 resulting in antiplatelet effects. Thus, patients being considered for surgery are at risk for bleeding, and in the preoperative period they should discontinue NSAIDs.[63] Glucocorticoids are also commonly used in patients with RA. Chronic use of glucocorticoids is associated with surgical site infections[64] and can result in poor healing of surgical site wounds.[65] It is thus advisable to taper glucocorticoids before surgery if feasible. Furthermore, in patients receiving long-term glucocorticoid therapy the hypothalamic-pituitary-adrenal axis is commonly suppressed. Patients taking greater than or equal to 20 mg of prednisone for 3 weeks or more may have adrenal suppression, which could result in hypotension and shock. In such circumstances patients should be given supplemental corticosteroids perioperatively to prevent adrenal insufficiency.[66]

Risk of infections after surgery is a major concern in patients with RA who are often immunosuppressed. For that reason, surgeons often request that RA therapies be discontinued before surgery. Most of the available data concern orthopedic surgery.[67,68] The use of hydroxychloroquine, methotrexate, and leflunomide is considered to be

safe in the perioperative period because studies have failed to identify an increased risk of infections.[69–73] However, because these studies focused mainly on joint-replacement surgery, results may not be generalizable to all surgical procedures. As far as use of bDMARDs, a large retrospective cohort study using Medicare and Truven MarketScan administrative data showed that the risk of infection requiring hospitalization and prosthetic joint infection were similar across biologic agents in patients undergoing total hip or knee arthroplasty.[68] An analysis of the Danish DANBIO registry showed a slightly increased risk of infection following total hip or knee arthroplasty (HR, 1.35 [0.65–2.80]) albeit not statistically significant in patients receiving bDMARDs compared with those that did not receive biologics.[67] The joint guidelines between the American College of Rheumatology and the American Association of Hip and Knee Surgeons recommend stopping bDMARDs and planning the surgery at the end of the dosing cycle.[74] For restarting bDMARDs, they recommend waiting for a period of typically 14 days following surgery when there is evidence of wound healing. They also provided guidance on tsDMARD tofacitinib and recommended withholding tofacitinib for 7 days before elective arthroplasty. Few studies have provided information on the safety of RA treatments on nonorthopedic surgical outcomes, and to our knowledge, none have specifically addressed oncologic surgery.[75,76] Increased infections and delayed wound healing are to be expected. For this reason, recommendations for general oncologic surgery at this time should follow those proposed for joint replacement.

Radiation

There has been a concern with the use of radiation in patients with autoimmune rheumatic diseases, primarily in those with systemic sclerosis, and to a lesser degree, in patients with systemic lupus erythematosus.[77,78] In general, RA is not considered a contraindication for radiation therapy. In a review of medical records of 131 patients with RA that received a mean of 45 Gy of radiation, no differences were found in acute effects, such as mucositis, dysphagia, and skin changes, and late effects, such as cardiac toxicity, small-bowel obstruction, and tissue fibrosis or necrosis in patients with RA compared with patients with non-RA connective tissue diseases receiving radiation.[79] In another study patients with breast cancer with RA who received a median of 60 Gy of radiation did not show a significant difference in acute or late toxicity, compared with patients without RA with breast cancer who received radiation.[80] However, a few case reports have shown adverse toxicities from radiation in patients with RA.[81,82] We recommend a cautious approach to the use of radiation in patients with RA until further data are available.

Chemotherapy and Other Drug Therapies

Although there are guidelines for the management of RA in patients with a cancer history, the American College of Rheumatology does not have any current recommendations for the management of RA in patients with active cancer.[47] There have been theoretic concerns that some DMARDs may suppress the immune system, which may adversely affect cancer treatment. There is a general consensus in clinical practice that bDMARDs should be held in patients with active cancer receiving chemotherapy to avoid an increase in adverse events, especially infections. Anecdotally, patients with RA receiving chemotherapy often have improvement in their disease activity because the chemotherapy agents used are immunosuppressive, and also because corticosteroids are often given with the chemotherapy infusions. Finally, csDMARDs and tsDMARDs can interact with other drugs, and this should be taken into consideration, not just with chemotherapeutic agents, but also with targeted cancer therapies, which can present important drug interactions (eg, imatinib and cyclosporine).

Immune Checkpoint Inhibitors

In the last decade, improvement in the safety and efficacy of several cancers with the use of immune checkpoint inhibitors (ICI) has led to Food and Drug Administration approval of several ICI. These agents target the cytotoxic T-lymphocyte-associated protein-4, programmed cell death protein-1, or programmed death ligand-1 pathways. Activation of the immune system with ICI agents can also result in unwanted and off-target inflammatory or autoimmune effects, commonly referred to as immune-related adverse events (irAE).[83,84] Inflammatory arthritis is the most commonly reported rheumatologic irAE.[85–87] Most often patients present with seronegative polyarthritis or oligoarthritis, but occasionally develop well-defined seropositive RA.[83] Generally speaking, these irAE occur late, can have varying presentation affecting small and large joints, and lower and upper extremities.[83,88–90] Most patients receive corticosteroids to treat their arthritis irAE but some may develop chronic arthritis requiring DMARDs for disease control.[90] The effects of immunosuppressive therapies for arthritis on cancer outcomes in patients receiving ICI remain largely understudied. However, a recent study showed that patients with cancer receiving TNFi for the treatment of corticosteroid-refractory irAE had lower survival compared with patients who received only steroids.[91]

Patients with preexisting autoimmune disease including RA have been excluded from clinical trials of ICI and hence the available evidence stems from observational research. In patients with preexisting RA, the rate of arthritis irAE is estimated to be up to 44%[83]; however, most studies evaluating flares of RA following ICI therapy in patients with preexisting RA have had small sample sizes.[92–97] Further research is needed to evaluate the effects of flares and therapies to manage flares on cancer outcomes.

SUMMARY

One in three people, including patients with RA, develop cancer over their lifetime,[98] and patients and providers are thus frequently faced with making complex decisions related to RA and cancer therapy. Overall, the risk of cancer does not seem to be increased for most DMARDs, other than some small safety signals seen with TNFi and the development of lymphoma and skin cancer. Treatment of RA in patients with cancer is complex. Conventional DMARDs can generally be used even in patients with active cancer if they are not receiving chemotherapy and there are no drug interactions. In general, in patients with active cancer the use of bDMARDs and tsDMARDs is not recommended, especially when they are receiving concomitant cancer therapies. In patients with premalignant conditions these agents can be used with caution if required to control disease activity, with careful monitoring and repeated screening. Patients with cancer can receive csDMARDs if there are no contraindications related to concomitant therapies. bDMARDs, especially TNFi, and tsDMARDs should be avoided in patients with recently diagnosed cancer, at least until treatment is completed. An exception is rituximab, which has generally been considered safe in patients with cancer. Biologics and tsDMARDs can be considered in patients with a prior history of cancer and no evidence of disease for at least a few years. In patients with advanced metastatic disease, quality of life considerations are crucial, and use of effective RA therapy including biologics should be considered to improve patients' well-being at the end of life.

Cancer treatment in patients with RA also needs special attention. Patients with RA undergoing surgery, radiation, chemotherapy, or immunotherapy need careful monitoring because they are more susceptible to adverse events from these treatments than patients without RA.

Given the complexities in the clinical management of patients with RA and cancer, a multidisciplinary approach is encouraged to enhance patient well-being without detriment in cancer outcomes. Given the importance of balancing quality of life and survival, patient preferences should always be taken into consideration. Choices about therapy should be consensual, using principles of shared decision-making to ensure that patients understand potential harms and benefits, and that their preferences and values are considered in the management plan.

CLINICS CARE POINTS

- Biologic and tsDMARDs can be considered in patients with a remote history of cancer, and no recurrences.
- Patient preferences and values should be considered in treatment decision making in patients with RA and cancer, with appropriate discussions on quality of life and survival trade-offs.
- Patients with RA receiving cancer therapy including chemotherapy, radiation, and/or immunotherapy should be monitored closely for toxicities.

DISCLOSURE

M.E. Suarez-Almazor has received consultant fees from Agile Therapeutics, AMAG Pharmaceuticals, and Gilead. X. Pundole, none.

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