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BOWEL DISEASE**

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**REVIEW ARTICLE: MALIGNANCY ON THIOPURINE TREATMENT WITH
SPECIAL REFERENCE TO INFLAMMATORY BOWEL DISEASE**

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Azathioprine

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Malignancy

Cancer

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Abstract

Background: Immunosuppression is a risk factor for carcinogenesis. Thiopurines specifically contribute to this. As thiopurines are used more aggressively in the treatment of IBD, it is likely that we will see more thiopurine-related malignancy.

Aim: To review the literature, exploring how immunosuppression, thiopurines specifically, might cause cancer and which malignancies occur in practice, placing specific emphasis on IBD cohorts.

Methods: Search terms included “malignancy” “cancer” “azathioprine” “mercaptopurine” “thioguanine” “thiopurine” and “inflammatory bowel disease” “crohn’s disease” “ulcerative colitis”. We also searched for specific cancers (lymphoma, colorectal cancer, skin cancer, cervical cancer) and reviewed the reference lists of the articles detected.

Results: Immunosuppression is associated with an increased risk of cancer. Thiopurines are associated with specific additional risks. In IBD cohorts very few thiopurine-related malignancies have been reported. However, studies suggest a relative risk of 4-5 for lymphoma. This still translates to a low actual risk, (one extra lymphoma in every 300-1400 years of thiopurine treatment).

Conclusion: Whilst we must be aware of this risk and counsel our patients appropriately, thiopurines remain a mainstay of IBD therapy. We present practical advice aimed at minimising our patients’ risk of developing malignancy, whilst optimising the benefits that thiopurines can provide.

Introduction

Azathioprine (AZA), mercaptopurine (MP) and tioguanine make up the group of drugs known as thiopurines. In the treatment of inflammatory bowel disease (IBD), AZA and MP are first line immunomodulatory agents, used to induce and maintain clinical remission, heal fistulae and minimise our patients' exposure to steroid treatment(1;2). Whilst generally safe and well-tolerated, the development of malignancy as a late complication of thiopurine-use in IBD is of concern for both physicians and patients. As thiopurines are used earlier, more frequently and more aggressively, with a new emphasis on disease rather than symptom control(3;4), it is likely that we will see the emergence of more serious adverse events such as malignancy, as the risks, as well as the benefits, of such a strategy will be higher.

The literature on malignancy in patients treated with thiopurines relies heavily on case series and retrospective studies, making judgements about the magnitude and specific nature of the risks difficult to ascertain. It is however, widely accepted that immunosuppression is a risk factor for the development of tumours and there is a substantial body of evidence that thiopurines specifically contribute to carcinogenesis. AZA is classified as a carcinogen by the International Agency for Research on Cancer (IARC)(5)

In this review we present an overview of the literature on the risk of malignancy associated with thiopurine treatment, including a brief overview of how immunosuppression and specifically thiopurines might cause cancer and the clinical literature to establish what occurs in practice. We place specific emphasis on studies conducted on IBD cohorts. We then draw from this data some practical advice, for

1
2 physicians and patients, about the risks and benefits of thiopurine
3 treatment and how any risk of malignancy might be minimised.
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7 A Pubmed search was performed from 1966 to Jan 2010. Search terms
8 included “malignancy” “cancer” “azathioprine” “mercaptopurine”
9 “thioguanine” “thiopurine” and “inflammatory bowel disease” “crohn’s
10 disease” “ulcerative colitis”. We also searched for specific cancers
11 (lymphoma, colorectal cancer, skin cancer, cervical cancer). Relevant
12 articles were reviewed, as were their reference lists to identify further
13 articles.
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20 21 **The immune system and carcinogenesis**

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23 It is almost 100 years since it was originally proposed that the immune
24 system had a role in identifying and eradicating cells with malignant
25 potential and 50 years since the first experimental evidence to support
26 this theory emerged(6). Although the initial models have been shown to
27 be simplistic, (with the immune system also promoting tumour
28 development in some contexts(7;8)), immune suppression is associated
29 with an increased risk of cancer.
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40 Many cancers develop on a background of chronic infection (e.g. human
41 papillomavirus 16 & 18 and cervical cancer; Epstein Barr Virus (EBV)
42 and lymphoma, Hepatitis B & C and hepatocellular carcinoma etc.) In
43 HIV and post-transplant cohorts, immune suppression is associated with
44 a huge excess of cancer cases of infectious aetiology(9;10) and the degree
45 of immune suppression is strongly associated to risk and prognosis of
46 overall malignancy in both contexts(11;12). A proportion of the risk of
47 malignancy attributable to thiopurine treatment will therefore be
48 common to all immunosuppressive treatments and unavoidable in the
49 current treatment of IBD.
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How might thiopurines cause cancer?

In addition to the effect of immune suppression, however, there are specific characteristics of thiopurines which may promote carcinogenesis. Thiopurines work by incorporation of “rogue” thiopurine nucleotides into DNA, but this subtly disrupts DNA structure(13), interferes with DNA replication and repair(13-15), creates unstable base pairs(16) and codes ambiguously, promoting mutagenesis(16).

Thiopurines also directly promote DNA damage by rendering it highly sensitive to radiation, particularly ultra-violet A (UVA) radiation, which accounts for 95% of UV radiation from sunlight. When thioguanine nucleotides are incorporated into DNA, the action of radiation creates reactive oxygen species which attack both the DNA, and its surrounding proteins, promoting mutagenesis (17-22). This is thought to account for the significant excess of non-melanoma skin cancer seen in those taking long-term thiopurines and the excess of brain tumours seen when leukaemia treatment with MP was combined with cranial radiotherapy(23).

Recent work has demonstrated *in vivo* that individuals with IBD treated with thiopurines have higher rates of somatic mutations in circulating white cells than thiopurine naïve patients(24). The rate of mutation was proportional to both the dose and duration of treatment and the pattern of mutations formed a specific thiopurine signature(24). Clinical data has linked the risk of malignancy during thiopurine treatment to total dose of azathioprine received(25;26), thiopurine metabolite levels and TPMT mutations(27-30). Comparing different post-transplant immunosuppression regimes has also implicated thiopurines(31-36), although this finding has not been universal(37). Specific cytogenetic

1
2 abnormalities occur in drug-induced AML on AZA treatment(38) and are
3 characteristic of azathioprine-associated skin cancers(39). All these
4 findings suggest that thiopurines are specifically involved in
5 carcinogenesis.
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10 11 12 13 14 **Risk of malignancy with other agents**

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16 As might be presumed from the paragraphs above, thiopurines are not
17 the only drug for IBD that are implicated in carcinogenesis.
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21 Although several large IBD series have failed to demonstrate a link
22 between tumour necrosis factor (TNF)- α blockers and an increased risk of
23 malignancy(40-43), a meta-analysis of the rheumatology literature
24 produced an estimated three-fold increase in malignancy, an effect which
25 appeared to be dose-related(44). A retrospective cohort of 7957 patients
26 treated for ocular inflammation also found a significant increase in
27 cancer-related mortality in those on TNF α -blockers but not for any other
28 immunosuppressant including azathioprine(45). In the IBD literature,
29 concerns have been raised about a possible association between TNF- α
30 blockers and an increased risk of lung cancer, including one report of a
31 patient who developed a lung tumour which expressed TNF- α and
32 regressed spontaneously on cessation of treatment(46). Similar concerns
33 were raised by a trial of TNF- α blockade in the treatment of chronic
34 obstructive pulmonary disease(47). This has lead to caution being
35 suggested in the prescription of TNF- α blockers in older smokers(48).
36 Reports of cases of both lymphoma and leukaemia potentially associated
37 with TNF- α blocker treatment are far in excess of what would be expected
38 if there were no link between the two(49;50). In particular, reports of
39 lymphoma occur nearly seven times more frequently than predicted(49).
40 A meta-analysis of the literature estimated that in clinical trials of TNF- α
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2 blockers lymphoma occurred at approximately 3 times the rate in the
3 general population (OR3.23, 95%CI 1.5-6.9) and 1.7 times the risk of an
4 IBD patient on immunomodulatory treatment (95%CI 0.5-7.1)(51).
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9 Methotrexate has less evidence of carcinogenic potential than either
10 biologics or thiopurines. Concerns were raised by an apparent excess of
11 lymphoma cases in those treated with methotrexate for rheumatoid
12 arthritis (RA), particularly as several cases were reported to be EBV-
13 positive and some regressed spontaneously when the methotrexate was
14 withdrawn(52). However, the population as a whole does not seem to
15 experience an excess of either lymphoma(52) or other malignancy(53)
16 and one reviewer estimated that only one in 3500 RA patients treated
17 with methotrexate would develop lymphoma(54). There is less evidence
18 in the IBD population but early suggestions are that single agent
19 methotrexate therapy does not increase the risk of malignancy in this
20 context(55-57).
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32 **Thiopurine-related malignancy in IBD cohorts**

34 **LYMPHOMA / LEUKAEMIA**

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36 The risk of lymphoma attributable specifically to thiopurines is difficult
37 to calculate, the available literature is summarised in table 2. There is
38 ongoing debate about whether IBD patients are already at an increased
39 risk, a serious confounding factor in retrospective studies, where those
40 with more aggressive disease and therefore a higher innate risk of
41 lymphoma are also those most likely to receive thiopurine treatment. In
42 keeping with this, large population-based studies (58-63) have generally
43 failed to show an overall association between IBD and lymphoma, whilst
44 series from tertiary centre clinics do demonstrate an increased risk(64-
45 67). The fact that a disproportionate number of the lymphomas which
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2 develop in IBD cohorts occur in the intestine also suggests that the IBD
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4 itself is involved in lymphoma development.(68)
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7 Series which have attempted to address the risk of thiopurines over and
8
9 above IBD itself have produced conflicting results, some finding no
10
11 association between thiopurine treatment and lymphoma in
12
13 IBD(59;60;63;69-71), but others suggesting an increased
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15 incidence(67;72-74). A meta-analysis of the available data produced a
16
17 relative risk of 4 for all lymphomas in patients with IBD on thiopurine
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19 treatment compared to those with IBD not receiving thiopurines(75). The
20
21 very low background incidence of lymphoma however means that this
22
23 still equates to a low absolute risk, which was estimated to equate to one
24
25 excess lymphoma in 300-1400 years of treatment(75). However, there
26
27 are subsets of the population in whom risks will be higher, most notably
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29 in older individuals where the background risk of lymphoma is higher.
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31 A French nationwide study including 19 486 patients with IBD recently
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33 published data suggesting higher rates of lymphoma in those patients
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35 currently receiving thiopurines, which drops to baseline once treatment
36
37 has been discontinued. They calculate a multivariate adjusted hazard
38
39 ratio of 5.28(2.01-13.9, p=0.0007) for lymphoma on thiopurine
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41 treatment.(68)
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43 In this series there was a clear association between the development of
44
45 lymphoma and EBV infection(68). EBV is a human herpes virus which
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47 can persist in B-lymphocytes, producing a variety of cell signals to
48
49 transform the host cell's behaviour. (See ref (76) for a more detailed
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51 explanation of the role of EBV in the development of lymphoma). EBV
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53 has been characteristic of lymphomas reported in other series (72;77-82),
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55 although this finding has not been universal(83). Again, the French
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2 group highlighted rare but serious reports of rapidly fatal post-
3 mononucleosis lymphoproliferative disease in young men(68).
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7 There has been recent concern about hepatosplenic T-cell lymphoma
8 (HSTCL) developing in IBD patients co-treated with infliximab and
9 thiopurines(84-87). To date, there are 24 reports of HSTCL in patients
10 receiving TNF- α blocking treatment for IBD(88-90). This aggressive
11 lymphoma has a very high mortality rate and seems to affect
12 predominantly young patients. It has been previously reported in the
13 context of solid organ transplantation as the consequence of a variety of
14 immunosuppression regimens(91) and may be related to viral
15 infection(91). There is ongoing debate about the wisdom of co-
16 prescribing infliximab and thiopurines, (a strategy thought to optimise
17 treatment outcomes) but which drug is primarily responsible, or whether
18 HSTCL is specifically related to co-prescription is not clear. The fact that
19 the problem seems to be specific to IBD does implicate co-
20 prescription(89). It is worth noting however, that there have been several
21 case reports of HSTCL in infliximab-naïve IBD patients on AZA(92-95)
22 and others where the infliximab seems distantly related to the
23 development of HSTCL(90). Reassuringly, the epidemic predicted when
24 the first series of HSTCL case-reports were published has not occurred,
25 despite increasing use of biologics in crohn's disease, and a recent meta-
26 analysis found that rates in co-treated individuals were equivalent to that
27 in those taking immunomodulation alone(96). However this area
28 remains one of particular concern.
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50 Further evidence which would support a causal role for thiopurines
51 includes an association between aggressive thiopurine treatment
52 (indicated by leucopaenia) and haematological malignancy(97) and a
53 case report of confirmed lymphoma in a CD patient which completely
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2 regressed when AZA was withdrawn(77). Specific karyotypes, thought to
3 denote a cytotoxic effect of thiopurines, in particular monosomy 7, have
4 characterised cases of leukaemia and myelodysplasia occurring on AZA
5 treatment(38;98;99).
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11 Overall there is probably a slightly increased risk of haematological
12 malignancy on thiopurines although the risks are generally outweighed
13 by the benefits of thiopurine treatment, see below(61;75;100).
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18 **COLORECTAL CANCER**

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20 Colorectal cancer (CRC) is a well established long-term risk of IBD,
21 known to be attenuated by long term aminosalicylate (5-ASA)
22 treatment(101). The effect of thiopurines on CRC risk has been harder to
23 ascertain and there has been concern that oxidative stress at sites of
24 inflammation could exacerbate thiopurines' carcinogenic potential(25).
25 Most evidence suggests however, that thiopurines are risk-neutral in this
26 context(71;101-106), although a recent study available in abstract
27 reports a cohort of 19438 IBD patients in whom there was a trend
28 towards protection against CRC with thiopurine use, which reached
29 significance for those with longstanding (>10yrs) extensive colitis(73).
30 Co-administration of 5-ASA was not corrected for however, which
31 introduces a possible confounding factor.
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44 **CERVICAL CANCER**

45 Since the majority of cervical cancers relate to HPV 16 & 18 infection,
46 there are concerns that immunosuppression could increase risk. Initial
47 reports suggested that, whilst an excess of cancers could not be
48 detected(63;107), there was an increase in cervical dysplasia in the IBD
49 population(108;109). However, this finding has been refuted by several
50 recent studies(110-113)
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2 A further increase in risk as a result of thiopurine therapy has also been
3 difficult to prove. One study (abstract only) suggested that treatment
4 duration with azathioprine could be a risk factor, although this failed to
5 reach significance(111). A large Canadian cohort did not detect a link
6 between single agent AZA/MP and cervical dysplasia or cancer, however
7 this subgroup was very small, containing only 13 patients from an
8 original study cohort of nearly 248000 women. On the other hand, those
9 that had cashed prescriptions for both steroids and an
10 immunomodulatory agent within the five year study period were at an
11 increased risk of cervical cancer (OR 1.41, 95%CI 1.09-1.81) and the use
12 of the oral contraceptive pill was a relevant risk factor (112). Meanwhile
13 a large tertiary centre series has confirmed that treatment with
14 azathioprine does not affect the risk of cervical cancer or dysplasia,
15 smoking was however associated with increased rates of cervical
16 dysplasia(113).
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31 Overall therefore, evidence would suggest that the risk of cervical cancer
32 in IBD is similar to that in the general population and is unaffected by
33 thiopurines.
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38 SKIN CANCER

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41 There is only one study addressing the risk of skin cancer in patients
42 with IBD. This study uses retrospective analysis of a US database,
43 including over 50 000 IBD patients each matched to 3 controls from the
44 general population. This study suggested that there was an increased
45 risk of non-melanoma skin cancer in the IBD population as a whole (IRR
46 1.64, 95%CI 1.51-1.78) and that thiopurine use during the last 90 days
47 increases this further, OR 3.56, 95%CI 2.81-4.50, (OR 4.27 95%CI 3.08-
48 5.92 for those with exposure of greater than 1yr). Biologic treatment was
49 also associated with increased risk (OR 2.18 95%CI 1.07-4.46).(114)
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2 Whilst significant, this is nowhere near the relative risks of up to 250
3 reported in transplant cohorts.
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5 6 7 **OTHER TUMOURS**

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9 The evidence for solid organ tumours seems to suggest no difference in
10 incidence between those who have and those who have not received
11 thiopurines for IBD(69-71;97;115;116). The occurrence of unusual
12 tumour types in patients receiving AZA is of concern, e.g. hepatocellular
13 carcinoma in patients with no background cirrhosis or viral
14 hepatitis(117-119) and squamous carcinoma of the rectum in an HPV 16
15 positive patient receiving long term MP.
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23 To date there is a paucity of data on the incidence of other tumour types
24 in IBD patients treated with thiopurines.
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28 29 **Balancing risks vs. benefits**

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32 Those studies which attempt to weigh the benefits of thiopurine use in
33 IBD against the risk of malignancy all conclude that thiopurines remain
34 a good treatment option for IBD(75;100;120). One study adopts a QALY-
35 based mathematical model to predict how much an immunosuppressant
36 would have to increase the chance of developing lymphoma before it
37 would be considered to be causing net harm(120). The cut off was
38 calculated at 10 times the general population risk (or 5 times the risk in
39 the IBD population). Whilst still coming down in favour of thiopurine
40 prescription, this is not that far from the relative risk shown in some
41 clinical series. Of course, such calculations are based on a number of
42 estimates and assumptions and one must also consider what alternative
43 treatment might be offered if thiopurine use were reduced.
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55 56 **Practical advice to doctors and patients**

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4 If we therefore accept that, despite the risk of malignancy, thiopurines
5 remain one of our best treatment options for IBD, what can we do to
6 minimise the risk of cancer? The advice outlined below is summarised in
7 table 1.
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10 11 12 **Patient Selection:**

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14 When prescribing immunosuppressive agents we must actively consider
15 the risk:benefit ratio for the individual patient in front of us, have a clear
16 treatment indication/goal and carefully monitor to ensure that this
17 benefit is being attained.
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23 Extensive research is currently being directed at identifying predictors of
24 severe and complicated IBD(121;122) which should assist us in
25 identifying those patients with the most to gain from aggressive
26 treatment. Meanwhile there are several groups in whom the risks of
27 treatment are higher. Older patients have been shown to have a
28 considerable excess risk of cancer on immunosuppression. In the renal
29 transplant literature a 6% increment in risk has been estimated for every
30 year increase in age(123). Those on multiple agents are also likely to
31 accumulate risk(75;124). Patients with a previous malignancy are a
32 logical group in which we should be cautious. Renal transplant
33 experience has led to tumours being classified as low, intermediate or
34 high risk for recurrence on immunosuppression(125). (Low risk:
35 lymphoma, testicular, uterine, cervical and thyroid cancers, and renal
36 cell cancers found incidentally in the explanted kidney. Moderate risk:
37 colon, breast, prostate, endometrial cancers and Wilm's Tumours. High
38 risk: bladder, renal cell and skin cancers, myeloma and
39 sarcoma)(125;126). Transplant guidelines suggest avoiding
40 immunosuppression until the patient has been one year free of cancer if
41 the tumour was low risk, two years for intermediate risk and up to five
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2 years in high risk tumour-types(125). In a cohort of patients
3 transplanted despite pre-existing prostatic cancer, those patients with
4 more advanced disease were at the highest risk of experiencing
5 recurrence(126). How this data relates to those on single agent therapy
6 for IBD is not known.
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12 Since TPMT deficiency and high TGN levels have been associated with an
13 increased risk of malignancy(27;28;30), those with TPMT heterozygous
14 deficiency should be treated with half standard dose(127) and all patients
15 should have steady state TGN levels monitored to allow dose-
16 adjustments to keep them within a therapeutic range(128;129). In this
17 regard, TGN monitoring assists not just in achievement of therapeutic
18 dosing but also detects over-treatment, allowing safe dose-reduction
19 which could reduce the occurrence of malignancies. In patients who are
20 failing to achieve the desired response, (despite adequate TGNs),
21 prescribers should have a low threshold for changing agents or switching
22 to low dose AZA with allopurinol co-therapy(130).
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34 **Treatment timing and duration:**

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36 The current move towards a “top-down” approach in the treatment of IBD
37 is likely to lead to greater thiopurine exposure. Concerns about
38 treatment risks need to be balanced against the improved outcomes seen
39 when patients are started on immunosuppression early in their disease
40 course(131;132).
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47 The decision to stop thiopurines can be difficult. Hopes that a four year
48 course of treatment would be adequate to achieve lasting remission(133)
49 have proved unfounded(1), long-term maintenance of remission seems to
50 require long-term treatment(134). Whether stopping thiopurine
51 treatment actually decreases a patient’s cancer risk also remains
52 unknown(75). However, the CESAME study strongly suggests that for
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2 lymphoma, at least, risk returns to baseline after cessation of thiopurine
3 treatment(68).
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7 Limiting immunosuppression prescribed alongside infliximab to reduce
8 lymphoma risk has been the subject of much recent debate. Van Assche
9 et al. demonstrated that stopping thiopurine co-treatment after 6 months
10 of regular infliximab has no impact on subsequent treatment
11 outcome(84). However, many reported HSTCL cases occurred early in
12 the infliximab treatment protocol, and would not have been avoided by
13 such a strategy(87) and there is concern that longer follow-up of these
14 patients may show a benefit of co-prescription, particularly as
15 withdrawal of concomitant immunosuppression has been associated with
16 reduced infliximab trough levels and a rise in C-reactive protein
17 levels(135).
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29 **Agent Selection:**

30 In future we may be able to avoid exposing patients with either a poor
31 chance of response or high risk of toxicity to thiopurines, by the
32 application of pharmacogenomics(136-138). TGN monitoring is perhaps
33 even more important. Of course in most patients, an adverse
34 pharmacogenetic profile for thiopurines would simply lead to prescription
35 of methotrexate or biologic treatment, both associated with their own
36 cancer risk. Other immunosuppressive agents such as sirolimus and
37 mycophenolate appear to be less carcinogenic(12) but as yet have little
38 evidence of benefit in IBD and are not suitable first line agents.
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49 **Screening/Surveillance:**

50 Since a proportion of malignancies associated with immunosuppressants
51 are also associated with viral infections, it makes sense to screen for
52 these before treatment is initiated. HPV, Hepatitis B & C, and EBV
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1
2 could be detected, treated or vaccinated against(139) before treatment
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4 began, in line with current ECCO guidelines(140).
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7 The incidence of PTLD in bone marrow transplant patients has been
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9 reduced by anti-virals and by giving EBV-negative blood products to
10
11 EBV-negative patients(141). However, this is unlikely to be cost-effective
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13 in IBD where the absolute incidence of lymphoma is so low. Transplant
14
15 guidelines suggest specialist surveillance for skin cancers and intensive
16
17 follow up for those with a previous lesion(142). Whilst rates in IBD are
18
19 not as high as in transplant cohorts, regular skin inspection by a
20
21 physician should be recommended(143) along with early treatment of
22
23 pre-malignant lesions(142).
24

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26 Renal transplant guidelines recommend annual cervical smears in
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28 females and prostate specific antigen (PSA) and rectal examinations in
29
30 males(142;143), however the IBD literature would not support this and
31
32 adherence to surveillance schemes for the general population should
33
34 simply be encouraged(12;142). Likewise, since thiopurines do not appear
35
36 to alter the risk of CRC in IBD, surveillance should be carried out
37
38 according to IBD(144) and population guidance (e.g.:
39
40 <http://www.cancerscreening.nhs.uk/bowel>)(145).
41

42 **Patient advice:**

43
44 We must be honest with our patients about the increased risk of cancer
45
46 with thiopurine exposure, but this advice needs to be placed strongly in
47
48 the context of the low absolute risks of malignancy and the potential for
49
50 significant benefit in terms of disease control. There is now a significant
51
52 literature addressing how patients weigh the benefits and risks of
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54 treatment options, some of which is specific to IBD(146;147). To enable
55
56 our patients to make a truly informed choice it may be beneficial to
57
58 develop specific decision-making tools(148).
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4 The avoidance of other carcinogens should be encouraged, such as
5 smoking cessation(143), avoidance of UV light and use of sun-protection.
6
7 The additional chemopreventive benefit of 5-ASA (at doses \geq 1.2g per
8 day(103)), should be explained.
9

10 11 12 **What to do if a patient develops cancer on treatment:**

13
14 If a cancer develops, thiopurines should be stopped. There are case
15 reports of immune-reconstitution effectively eradicating malignancy in
16 the absence of other therapy(77;149;150). This is particularly important
17 where the malignancy is related to an infectious agent(143).
18 Discontinuing thiopurines may have serious consequences on IBD
19 control, and non-immunosuppressive treatments (aminosalicylates,
20 nutrition, antibiotics, surgery etc.) must be optimised. However loss of
21 disease control may be unavoidable, indeed transplant recommendations
22 propose ceasing immunosuppression even if this results in graft
23 rejection.(124)
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34 **Conclusion**

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36 In conclusion, AZA and MP treatment in IBD are associated with an
37 increased risk of malignancy, attributable to both immunosuppression
38 and specific properties of thiopurine drugs. The risk appears to be most
39 significant for lymphoma, but the absolute risk remains low and
40 risk:benefit analysis supports the continued use of these agents for IBD.
41 We present practical advice for medical practitioners prescribing
42 thiopurines to help minimise their patients' risk of developing
43 malignancy whilst optimising the benefits that these drugs can provide.
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Table 1: Guidance to prescribers

The following guidance is all based on expert opinion. To date there is no evidence in the literature that any of these interventions will reduce the occurrence of cancer in patients on thiopurines. Until such evidence exists however, this constitutes pragmatic advice for those concerned with minimising the risk to their patients on thiopurines.

Issue	Guidance
Patient selection	Ensure clear indication and treatment goal Caution in elderly, previous malignancy, multiple agents
Pre-treatment	TPMT testing (and dose accordingly) HBV/HPV serology – consider vaccination Patient information on: <ul style="list-style-type: none"> • relative risk • sun avoidance/protection • adherence to population screening • adherence to IBD CRC surveillance • chemoprevention (5-ASA, ?folic acid) • smoking cessation
During treatment	Monitor and dose-adjust (from 4 weeks) to therapeutic levels, (200-400pmol/8x10 ⁸ RBC). Avoid repeatedly high TGN levels. Set timely review of efficacy with a view to changing agent if necessary (5-6/12)
Treatment cessation	Consider stopping thiopurine co-prescription with infliximab at 6-12 months. Stop thiopurine if a cancer develops. Consider treatment cessation in long term remission (>4yrs)

1
2 Figure 1:
3 Summary of thiopurine mechanisms of action.
4 Effects caused by incorporation of thioguanine nucleotides into DNA are
5 shown in blue and other effects in green. The red circles highlight
6 potentially carcinogenic aspects of these effects.
7

8 Abbreviations:

9 DNA – deoxyribonucleic acid

10 GTP – guanine triphosphate

11 MeMP – methylmercaptopurine

12 MMR – mismatch repair

13 TRAIL – Tumour necrosis factor-related apoptosis inducing ligand
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Table 2: Risk of lymphoma in patients with IBD treated with thiopurine agents.
The design of many of these studies did not allow calculation of OR.

Study	Context	number of patients	of lymphoma cases	increased risk?	OR / SIR / HR	95%CI	p-value
Connell 1994 (69)	tertiary centre database	755 all on thiopurine	zero	no			
Loftus 2000 (59)	tertiary centre retrospective	454 + search of referrals totalling 15000	1+ 46	no			
Farrell 2000 (67)	tertiary centre database	782 pts 238 on immunomodulators	4 cases all on immunomodulator inc. 2 on thiopurine	yes	31.2	2-85	p<0.0001 for all immunomodulators
Bernstein 2001 (63)	population database	6027 pts 60000 controls thiopurine status unknown	9 in whole cohort, none on thiopurine	no			
Lewis 2001 (60)	population database	16996 pts 60506 controls 1465 on thiopurine	18 cases in IBD patients inc. 1 on thiopurine	no	1.27	0.03-8.2	
Dayharsh 2002 (72)	tertiary centre series	17654 pts thiopurine status unknown	18 lymphoma cases	yes	2 fold increase		
Fraser 2002 (71)	tertiary centre retrospective	2204 pts 626 on thiopurine	8 including 3 on thiopurine	no			
Warman 2003 (70)	tertiary centre database	410 all on thiopurine	3 cases	no			
Beaugerie 2009 (73)	nationwide prospective cohort	19486 pts 5867 on thiopurine	23 cases inc. 15 on thiopurine	yes	5.28	2.01-13.9	p=0.0007
Armstrong 2010 (74)	population database	15471 patients	15 cases	yes	3.22	1.01-10.18	

Study Highlights

- Thiopurines promote malignancy both directly by DNA disruption and by immunosuppression
- In IBD, thiopurines increase lymphoma risk 4-fold, although the absolute risk remains low
- In IBD, thiopurines do **not** appear to increase the risk of cervical or colorectal cancer
- For other cancers there is a theoretical but unproven increased risk in the context of IBD
- Careful thiopurine prescription and monitoring, with appropriate patient advice, may reduce risk

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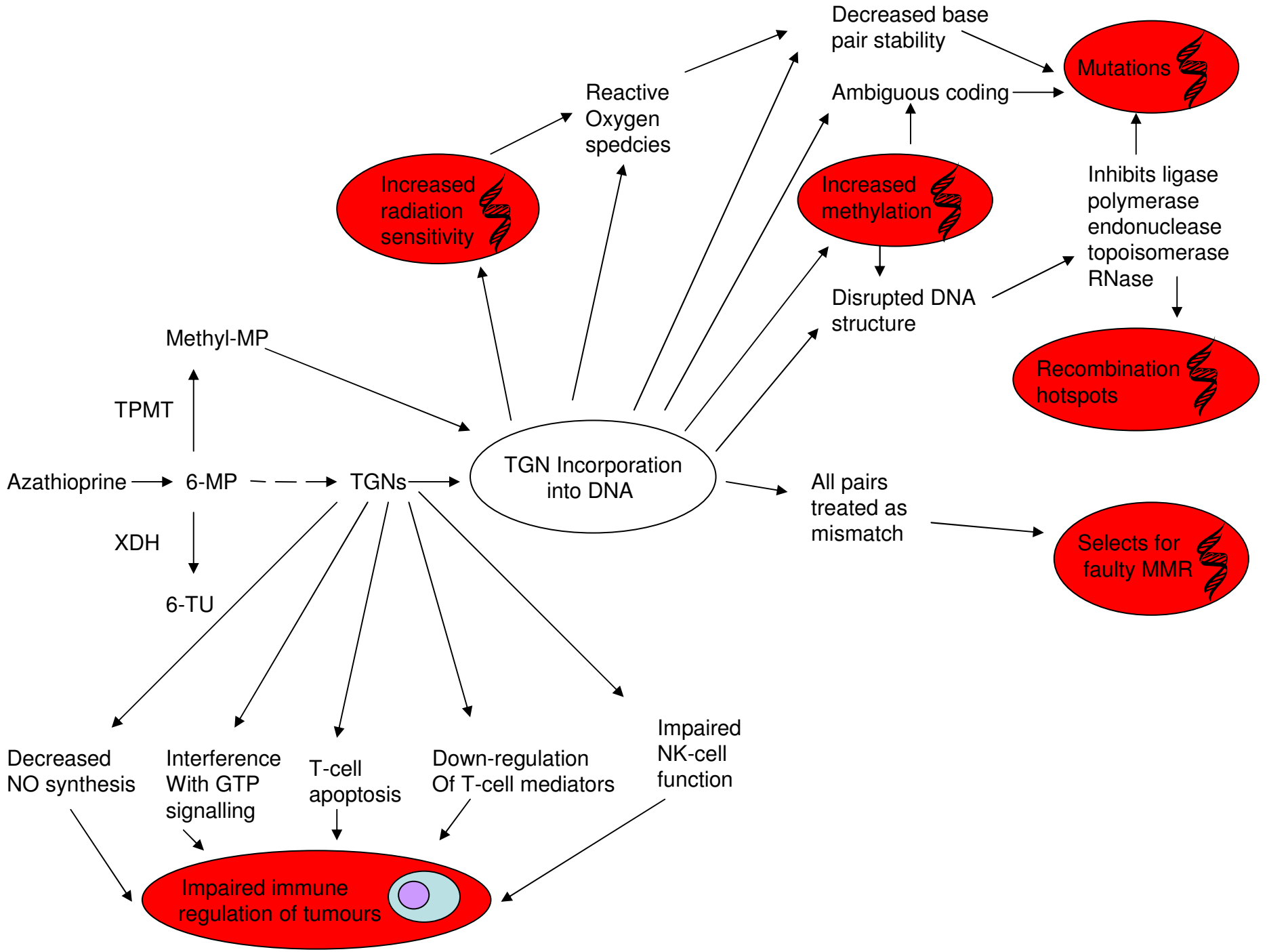
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