Effects of opioids on immunologic parameters that are relevant to anti-tumour immune potential in patients with cancer: a systematic literature review

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Background: The immune system has a central role in controlling cancer, and factors that influence protective antitumour immunity could therefore have a significant impact on the course of malignant disease. Opioids are essential for the management of cancer pain, and preclinical studies indicate that opioids have the potential to influence these tumour immune surveillance mechanisms. The aim of this systematic literature review is to evaluate the clinical effects of opioids on the immune system of patients with cancer.

Methods: A systematic search of Ovid MEDLINE (PubMed) and Embase, Cochrane database and Web of Knowledge for clinical studies, which evaluated the effects of opioids on the immune system in patients with cancer, was performed.

Results: Five human studies, which have assessed the effects of opioids on the immune system in patients with cancer, were identified. Although all of these evaluated the effect of morphine on immunologic end points in patients with cancer, none measured the clinical effects.

Conclusions: Evidence from preclinical, healthy volunteer and surgical models suggests that different opioids variably influence protective anti-tumour immunity; however, actual data derived from cancer populations are inconclusive and definitive recommendations cannot be made. Appropriately designed and powered studies assessing clinical outcomes of opioid use in people with cancer are therefore required to inform oncologists and others involved in cancer care about the rational use of opioids in this patient group.

The innate and adaptive immune systems provide crucial protection against pathogenic organisms and cancer (Gaspani et al, 2002; Shavit et al, 2004; Nüssler et al, 2007). Cancer immunosurveillance involves natural killer (NK) cells that have an inherent (innate) capacity to recognise and kill tumours via cell surface molecules (Table 1), the secretion of immunoregulatory cytokines and the actions of white blood cell (lymphocyte) subsets, which control and regulate anti-tumour immunity (T ‘helper’ or CD4+ T cells) or recognise and kill transformed cells (‘cytotoxic’ T or CD8+ T cells) (Table 1) (Foulds et al, 2013).

The importance of immunosurveillance in the context of cancer has been illustrated by a number of findings. High NK cell cytotoxicity and high concentrations of cytotoxic T cells are associated with a reduced progression of disease and better survival in patients with colorectal cancer (Nüssler et al, 2007; Pages et al, 2009). In contrast, rodent studies using the MADB106
It is becoming apparent that an individualised approach to cancer pain treatment is essential, as the analgesic properties and side effects of opioids exhibit great interindividual variability (Ahmedzai, 2013), as do their influence on immune cell function (Thomas et al., 1995; Jacobs et al., 1999). Furthermore, even if opioids were to have immunomodulatory effects in patients, this would only be of clinical interest and relevant to prescribers if these significantly influenced tumour growth, metastasis, infection and/or other clinical outcomes.

We have identified five studies that evaluated the effect of opioids on immune function in patients with cancer. However, the literature indicates that only the effect of morphine has been evaluated, and none of the studies have reported on relevant clinical end points.

**Table 1. Role and activation pattern of the main immune cells**

| Cell                | Role                     | Activators                                                                 | Mechanism of activity                                                                 | Arm  |
|---------------------|--------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------------|------|
| Dendritic cell      | Antigen presentation     | Multiple, including bacterial products and cytokines                      | Presentation of antigenic peptides in the context of MHC class I and II molecules and the delivery of essential costimulatory molecules | Innate |
| Natural killer cell | Anti-tumour Anti-viral   | Multiple, including the lack of MHC class I expression                     | Release of cytotoxic molecules (granymes, perforin)                                    | Innate |
| Neutrophil          | Anti-bacterial/-fungal   | Opsonisation                                                               | Phagocytosis and oxidative burst                                                      | Innate |
| Monocyte–macrophage |                          | Opsonisation                                                               | Phagocytosis and oxidative burst                                                      | Innate |
| lineage             | CD4⁺ T cell              | Immune coordination/ regulation Antigenic peptides presented by MHC class II plus essential costimulatory molecules | Regulating the activity of other immune cells                                          | Adaptive |
|                     | CD8⁺ T cell              | Cytotoxicity                  Antigenic peptides presented by MHC class I                              | Induction of apoptosis by (i) release of cytotoxins (perforin, granulysin, granymes), (ii) direct cell–cell contact, by upregulating surface Fas ligand | Adaptive |
| B cell              | Antibody production      | Antigens binding to surface immunoglobulin with help from CD4⁺ T cells     | Antibody production                                                                   | Adaptive |

**Abbreviations:** CD = cluster of differentiation; MHC = major histocompatibility complex.

**(mammary adenocarcinoma) cell line have shown that tumour burden can increase if NK cell cytotoxicity is reduced (Gaspani et al., 2002; Shavit et al., 2004). Furthermore, the incidence of secondary cancers is higher in patients who have had chemotherapy for a primary cancer (Morton et al., 2013). The effect of immune system impairment can also be selective, as there is a higher incidence of non-Hodgkin’s lymphoma, lip cancer and melanoma in transplant recipients on immunosuppressive treatment, whereas the incidence of leukaemia, lung, kidney and urinary tract cancers remained the same (Van Leeuwen et al., 2010).**

The central role that the immune system has in protecting against cancer means that any factors that influence protective anti-tumour immunity are likely to have a profound impact on the course of disease. Although opioids are essential for the management of cancer pain, numerous *in vitro*, animal and volunteer models have reported opioids to have a number of immunoregulatory effects. These are dependent on the opioid being tested, the component of the immune system that is being influenced, the administration schedule and also the experimental model (Van Der Laan et al., 1996; West et al., 1997; Martucci et al., 2004). Given the evidence that opioids have the capacity to influence anti-tumour immunity, it is important to better understand the potential clinical impact of opioid usage in this context.

Although the immune effects of opioids in patients with cancer have been reviewed previously (Budd, 2006; Pergolizzi et al., 2008; Sacerdote, 2008), there has been no systematic review of the literature assessing the effects of opioids on anti-tumour immune potential in patients with cancer and how these effects could influence the clinical management. The immunologic consequences of opioids that are administered to patients with chronic cancer pain over a period of several months are likely to be very different to those that are induced by the relatively short treatments that are administered to healthy volunteers or patients post-surgery, because of the differing immunologic phenotypes of these groups (Snyder and Greenberg, 2010; Colvin et al., 2012; Heaney and Buggy, 2012; Foulds et al., 2013; Gallizia et al., 2013). We therefore conducted a new systematic review of the literature relating to the effects of a broad range of therapeutic opioids on immunologic parameters that are relevant to protective anti-cancer immunity in non-surgical clinical studies.
In addition to the electronic search, reference lists from identified reviews and key publications were manually searched. Articles were also identified through searches of the authors’ own files, previous reviews on opioid-induced immunosuppression and outputs from prominent researchers in the field. Only papers published as full-text articles in English were reviewed. Surgical studies, patients undergoing cancer surgery, healthy volunteer studies and animal studies were excluded from this systematic review, as these groups have different opioid usage, immune system activation and receptor expression compared with patients on long-term opioids for cancer pain (Snyder and Greenberg, 2010; Colvin et al, 2012; Heaney and Buggy, 2012; Fouls et al, 2013; Galizia et al, 2013). Patients undergoing surgery are also exposed to a range of drugs during the operation, which potentially impact on immune function (Colvin et al, 2012; Heaney and Buggy, 2012). Furthermore, the effect of opioids in patients undergoing cancer surgery has been reviewed elsewhere (Colvin et al, 2012; Heaney and Buggy, 2012). As the data are only relevant if opioids have significant clinical effects, we specifically looked for articles that assessed clinical effects.

Two authors (JB and KM) undertook independent electronic literature searches and reviewed all titles and abstracts. Full papers were retrieved for those fulfilling the criteria, and also for those publications for which the ability to assess their eligibility could not be assessed on the basis of the titles and abstracts alone. Two review authors (JB and KM) then assessed the full text of all potentially relevant studies. Disagreement at all stages was resolved by consensus and with recourse to a third review author (AGP).

Data extraction, assessment and analysis. JB and KM independently extracted data regarding study design and results and assessed their quality. Data extracted were the type of study, study setting, study population (cancer type, stage, treatment) opioid used, dose and clinical outcome measures (e.g. survival). The methodologic quality of each study was independently assessed by JB and KM using Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews (QUADAS-2) (Whiting et al, 2011).

RESULTS

This systematic review of the effects of therapeutic opioids on immune function in patients with cancer identified five studies that were eligible for inclusion (Table 2). All were found to be prospective observational studies and no randomised controlled trials have been undertaken. These clinical studies have focused on the effects of opioids on markers of immune function, rather than on relevant clinical outcomes. All studies examined the effects of morphine – no other opioids have been investigated.

The quality of studies was determined using a QUADAS-2 analysis (Whiting et al, 2011). Included studies had a low risk of bias (patient selection, index test and flow and timing) and an unclear risk of reference standard. The two studies by Provinciali et al (1991, 1996) had an unclear patient selection risk. All studies had a low risk for applicability concerns (patient selection, index test and reference standard).

Makimura et al (2011) attempted to find markers that could predict resistance to morphine treatment by examining the plasma concentrations of 26 cytokines before and after morphine treatment in 44 patients with metastatic cancer (Table 2). They observed interindividual variability in baseline plasma cytokine concentrations and found no significant changes in the levels of
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Table 2. Summary of the effect of opioids on immune function in patients with cancer

| Author (year) | Research question | Patient population | Study design and method of recruitment | Interventions (opioid and doses) and comparator | Assoc. between opioid and immune function |
|---------------|-------------------|-------------------|----------------------------------------|-----------------------------------------------|------------------------------------------|
| Makimura et al (2011) | Are plasma cytokine levels potential biomarkers for predicting resistance to morphine treatment in opioid-naive cancer patients? | 44 Patients Age 69 (40–85) years 50% Men 93% Metastatic cancer PS status 1 (20%), 2 (55%), 3 (23%), 4 (2%) | Prospective observational study Cytokines measured at baseline and compared with samples after 8 days of opioid treatment Morphine straited as per a standardised protocol (dose not specified) | Morphine – doses not specified Patients acted as own controls, baseline samples compared with day 8 | None (except MIP-1α level decreased (P = 0.03) but multiple comparisons) (baseline: 7.2 ± 19.3 pg/ml vs day 8 2.3 ± 7.4 pg/ml) Plasma IL-12 (p40) level decreased nonsignificantly (P = 0.07) (baseline: 7.0 ± 17.4 pg/ml, day 8: 2.7 ± 7.6 pg/ml) No clinical end points measured |
| Hashiguchi et al (2005) | Do morphine and its metabolites modulate immune function in advanced cancer patients? | 14 Patients Age 28–76 years 53% Men Mixed-stage IV cancers (including breast, tongue, sarcomas) PS – not documented Group 1: 6 patients, opioid naive Group 2: 8 patients on morphine for 1 month | Prospective observational study Bloods at enrollment (phase 1), 1 week after starting or changing morphine dose/route (phase 2) and 2 weeks after phase 2 (phase 3). Phase 2 was between 10 and 21 days after phase 1 Limitations – 1 patient in group 2 excluded from phase 2 analysis; 2 in group 1, and 4 in group 2 excluded from phase 3 analysis due to deterioration | Group 1, final morphine dose 20–30 mg (routes: oral, intravenous) group 2: starting morphine dose 40–120 mg (oral, intravenous, subcutaneous, rectal) Patients acted as own controls | Negative correlation in Group 1 between morphine, M3G and M6G and immunoglobulin’s and PHA-induced lymphocyte proliferation but not NK cell activity or CD4/CD8 ratio Poor correlation for all immunologic markers in Group 2 No clinical end points measured |
| Provinciali et al (1991) | How does morphine affect NK and LAK cell activity in neoplastic patients? | 20 Patients with cancers of different origins (including breast, lung, ovarian and prostate) Age, gender, cancer stage, and PS status not reported | Prospective observational study Blood analysed 1 month after starting treatment and compared with healthy volunteers (transfusion centre) Limitations – no baseline analysis | N = 9 p.o. morphine ± 30 mg per day N = 6 i.t. morphine patients 4 ± 1.5 mg per day N = 5 opioid-naive patients Three patients acted as own controls from p.o. morphine to subsequent i.t. treatment Blood from healthy subjects provided by transfusion centre | Sig reduced NK cell activity (P < 0.05) NK cell activity reduced further with i.t. than p.o. LAK cell activity significantly increased LAK cell activity higher in p.o. than i.t. (P < 0.005) No clinical measurements |
| Provinciali et al (1996) | How does short- or long-term morphine administration affect NK/LAK activities? | 18 Patients (breast, lung, ovary, prostate, bladder, colon, larynx, stomach and kidney cancer) Age, gender, cancer stage and PS status not reported 10 patients treated with morphine 8 patients had no opioids | Prospective interventional study Short term – 1 patients treated with i.v. 10 mg morphine (4 pretreated with 5 mg p.o. bromocriptine). Blood checked at baseline and after 30 min Long-term p.o. morphine (90 ± 30 mg) for 1 month Limitations – 8 controls law/no pain, 10 active patients had high levels of pain | Morphine:10 mg i.v. in short-term study 90 ± 30 mg per day p.o. for 1 month in long term study N = 8 opioid naive cancer patients as controls | Short term: Cytotoxicity of NK cells reduced 113 ± 62 vs 44 ± 44 LU/µl × 10⁷ (P = 0.01) Increased LAK activity 169 ± 45 vs 252 ± 62 LU/µl × 10⁷ (P = 0.02) No change in the number of peripheral lymphocytes or % CD3, CD4, CD8, CD16, CD56 T cells Long term: NK cell activity reduced in morphine group vs those not treated 89 ± 23 vs 171 ± 27 LU/µl × 10⁷ (P < 0.001) Higher LAK activity in morphine-treated Daudi: 1581.5 ± 1325.0 vs 408.0 ± 24.15 (P = 0.04) K562: 4420.4 ± 3351.2 vs 1229.0 ± 1643 (P = 0.02) Higher % of CD3± and CD4± increased in morphine-treated CD3 (%): 50 ± 4 vs 44 ± 8 (P < 0.05) CD4 (%): 31 ± 3 vs 25 ± 5 (P < 0.05) % CD8± not affected by morphine treatment 12 ± 1 vs 13 ± 3 |
any cytokine (including interleukin-2 (IL-2)) after 8 days of treatment with morphine in previously opioid naive patients. This contrasts with the study by Palm et al (1998), which showed that the synthesis and secretion of IL-2 by lymphocytes increased significantly after 4 weeks of morphine treatment in 10 patients with chronic pain (including three with cancer). No clinical end points, for example, cancer progression- or disease-free survival were evaluated in either study (Palm et al, 1998, Makimura et al, 2011). This may suggest that the acute effects of opioids (over days) on the immune system differ from those that are induced following chronic exposure (over weeks).

The possibility that the immunologic consequences of opioids (morphine) depends on the nature of the exposure has been confirmed in a study of 15 patients with advanced cancer by Hashiguchi et al (2005) (Table 2), which reported that the impact of opioids on immune function might correlate with the duration of opioid administration. They found a negative correlation between the levels of morphine metabolites and circulating immunoglobulin levels and the in vitro proliferation of peripheral blood lymphocytes in response to phytohaemagglutinin (a non-specific activator of T cells) in patients who had just commenced on morphine. In contrast, no such effects were observed in patients who had been on morphine for over 1 month. Once again, no clinical parameters were measured.

Patients with a variety of cancers (including breast, lung, ovarian and prostate) on oral or intrathecal morphine have been reported to exhibit a lower NK cell activity and increased lymphokine-activated killer (LAK) cell activity than untreated or healthy controls (Table 2; Provinciali et al, 1996). The observation that intrathecally delivered morphine had a more profound effect than oral morphine suggests an important role for a centrally mediated effect. However, only a very small number of patients was studied and no clinical correlates were investigated (Provinciali et al, 1991). In a subsequent study, Provinciali et al (1996) determined the short-term immune effects (at 30 min) after a single 10 mg intravenous dose of morphine and the long-term effects after 1 month of oral morphine (90 ± 30 mg per day) on NK and LAK cell cytotoxicity in 18 patients with cancer (including breast, lung, ovary and prostate). These cytotoxicity responses were compared with baseline measurements, and those that were present before opioid treatment in the short-term experiments and in cancer patients not on opioids in the long-term study. This study demonstrated that both acute and chronic morphine administration reduced NK cell activity and increased LAK activity. Chronic morphine administration has also been shown to increase the proportion of CD3⁺ and CD4⁺ T cells in peripheral blood mononuclear cell preparations, whereas the prevalence of CD8⁺ T cells is unaffected and the proportion of CD16⁺ cells in peripheral blood mononuclear cell preparations, whereas the prevalence of CD8⁺ T cells is unaffected and the proportion of CD16⁺ lymphocytes is reduced. CD16 is a member of the Fc receptor family that is instrumental for the induction of antibody-dependent cellular cytotoxicity (ADCC). Antibody-dependent cellular cytotoxicity is a mechanism of cell-mediated immune defence and a decrease in the presence of such cells might therefore negatively impact on tumour surveillance. None of these parameters were affected during acute morphine administration (Provinciali et al, 1996). The number of patients in this study was also small, their cancers were different and once again no clinical measurements of tumour progression or survival were measured.

In summary, the studies included here suggest that the influence of morphine on immune potential could be dependent on whether it is administered acutely or chronically, the route of administration and also the immune parameters that are considered. These observations cannot be extrapolated to all opioids due to the heterogeneous physicochemical and pharmacologic properties of this broad class of drugs (Sacerdote et al, 1997; Keiser et al, 2009). Furthermore, the most important outcome – the clinical impact of these immune influences on cancer progression and patient survival – remains unexplored.

**DISCUSSION**

The management of pain is essential, as its immunosuppressive properties can influence cancer growth in animal models (Page et al, 2001; Gaspani et al, 2002; Page, 2003, 2005). Fears of precipitating serious toxicity and the risk of dependence and...
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The immunoregulatory effects of morphine and some other opioids can also be elicited by direct effects on immune cells expressing non-opioid receptors such as Toll-like receptor 4 (TLR4) (Wang et al., 2002; Borner et al., 2008, 2009; Keiser et al., 2009; Hutchinson et al., 2010; Franchi et al., 2012). Opioids can also have indirect effects that manifest via centrally produced mediators such as immunosuppressive glucocorticoids that are released as a consequence of hypothalamic pituitary adrenal axis activation, and via effects on the sympathetic nervous system, which innervates lymphoid organs (Figure 3; Wang et al., 2002).

Studies in rats have reported that oral morphine can suppress T- and B-cell proliferation and NK cell activity (Van Der Laan et al., 1996; West et al., 1997). Conversely, rodent models have shown that tramadol, but not morphine, dose-dependently increases NK cell cytotoxicity. Furthermore, tramadol, but not morphine, reduces lung metastasis following the injection of MADB106 mammary tumour cells into rats (Gasparsi et al., 2002). The capacity of tramadol to enhance immunity might be because of its coexisting intrinsic serotonergic effect (Sacerdote et al., 2000; Gasparsi et al., 2002). In mice, a single subcutaneous dose of fentanyl, but not buprenorphine, decreases lymphoproliferation in response to the mitogen concanavalin A, but has no effect on NK cell cytotoxicity (Martucci et al., 2004). A continuous infusion of fentanyl has been shown to decrease lymphoproliferation and NK cell cytotoxicity at 24 h, with NK cell cytotoxicity normalising by day 3. However, tolerance to the effects on lymphoproliferation did not develop until day 7 in these studies (Martucci et al., 2004). Buprenorphine had no such effects. In a rodent surgical model, a

Figure 2. Quadrangulation of the effects of opioids on pain, immunity and cancer. Under normal circumstances opioids inhibit pain, which is itself immunosuppressive (Page et al., 2001; Page, 2003). Some opioids also have specific effects on immune function, either suppressive or stimulatory, and the balance of these opioid-mediated effects influences the progression of cancer (in animal models) (Gasparsi et al., 2002). The immune system, via microglia and cytokines, influences the pain state (Hutchinson et al., 2008). Activated immune cells can also produce endogenous opioids, as well as morphine (Stein and Lang, 2009; Glattard et al., 2010). Cancer can also cause pain, by nociceptive, neuropathic and inflammatory mechanisms. There is a dynamic interaction of the immune system and cancer with immunodepletion and immunosculpting (Reiman et al., 2007). Furthermore, there are non-immune effects of opioids on cancer cells (Gach et al., 2011). All of these factors combine to create the net balance of cancer cell growth or destruction (Page, 2005). The white arrows indicate a beneficial effect on pain, immunity and cancer, and the solid arrows indicate a detrimental effect on immunity and cancer.

Opioids

Brain

ACUTE

CHRONIC

Anterior hypothalamus

Opioids

Peripheral effector

Lymphoid organs

Glucocorticoids

Brain

ACUTE

CHRONIC

Anterior hypothalamus

Opioids

Peripheral effector

Lymphoid organs

Glucocorticoids
single dose of fentanyl increased suppression of NK cell activity and resulted in more lung metastasis following the injection of MADB106 tumour cells (Forget et al, 2010). Although NK cell cytotoxicity in healthy volunteers is suppressed by morphine (Yeager et al, 1995), fentanyl has been shown to increase the number of circulating NK cells and NK cell cytotoxicity (Jacobs et al, 1999; Yeager et al, 2002).

Although clinically relevant concentrations of morphine and methadone have been shown to inhibit cytotoxicity of NK cells from rats, monkeys and pigs (Molitor et al, 1992; Condevaux et al, 2001), such effects have not been seen in healthy volunteers, with in vitro studies indicating that clinically relevant concentrations of morphine, methadone, fentanyl and diamorphine do not influence NK or T cells (Yeager et al, 1992; House et al, 1995, Thomas et al, 1995; Jacobs et al, 1999; Boland et al, 2013).

The preclinical data indicate that tramadol might be potentially stimulating of the immune response (Gaspani et al, 2002) and buprenorphine to be immune neutral (Martucci et al, 2004), however until there are comparative studies with clinical end points, no one opioid can be strongly recommended over another in terms of their immune effects. Furthermore, cancers will have differential effects on the immune status and immune regulatory profiles and responses in one patient might not be broadly applicable to all.

CONCLUSIONS

All studies discussed in this systematic review were prospective and observational. They all used morphine and no study reported the effects on clinical end points. Although the studies included in this review add to the current body of knowledge of opioid effects on the immune system, these findings cannot currently be extrapolated to cancer patients on chronic opioids for pain owing to differences in immune cell activation and opioid receptor expression (Borner et al, 2008). As a consequence, there is currently insufficient evidence on which to base a more rational choice of opioids for optimising pain control without negatively impacting on the patient’s essential protective immune function. It is therefore hoped that clinically derived data will provide better evidence in the future. In the meantime, judicious doses of opioids should continue to be used as part of a multimodal approach for the management of patients with cancer pain.

AUTHOR CONTRIBUTIONS

JB and KM undertook the literature search and contributed to study design, data collection and data analysis. JB provided the figures. AGP contributed to the study design. All authors were responsible for the writing and approval of the final report.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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