Dipartimento delle Units Multispecialistiche e dei Trapianti – Area: Gastroepatologica
U.O.C. Gastroenterologia ed Endoscopia -
Direttore: Prof. Maurizio Vecchi Tel. 02 55033326 – mail: maurizio.vecchi@policlinico.mi.it

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SAFETY OF METHOTREXATE TREATMENT IN PATIENTS WITH CROHN DISEASE AND PREVIOUS CANCER

Marina Coletta, Giovanni Casazza, Maurizio Vecchi, Flavio Caprioli

1. Background

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions of the gastrointestinal tract. As known, IBD patients display an increased risk of malignancy, similarly to subjects affected by other chronic inflammatory conditions (1). There is an increased risk of extraintestinal malignancies, including hematological malignancies and melanoma (2). Unexpectedly, the correlation between IBD and gastrointestinal malignancies is weak, probably related with the increasing implementation of endoscopic screening programs in colonic IBD. On the other hand, the wider use of immunosuppressive drugs might be involved in the reduction of colorectal cancer incidence and in the increasing frequency of hematological malignancies, respectively [3-4].
Several immunosuppressant drugs are routinely prescribed in IBD treatment, including anti TNF antibodies (infliximab, adalimumab, golimumab), thiopurines (azathioprine and 6-mercaptopurine) and methotrexate.
Several studies have evaluated the role of thiopurines in cancer development, demonstrating the connection between their use and non melanoma skin cancer (NMSC), lymphoproliferative disorders and myelodisplastic syndromes [5-9]. particularly, a large study by Beaugerie et al. demonstrated that the risk of recurrent cancer in patients with IBD and previous cancer is increased compared with patients without a previous cancer; however, this risk is not increased by immunosuppressive treatments, mainly thiopurines (10).
Controversial data are available about anti-TNF therapy and cancer because patients with prior cancer are usually excluded from clinical trials, and currently available guidelines usually suggest not to prescribe these patients immunosuppressive treatments. A recent multicenter US study described no increased risk of incident cancer in patients with a history of previous cancer treated with anti-TNF and followed up for 5 years compared with patients not treated with immunosuppressants [11].

Methotrexate is less commonly prescribed in IBD patients. Guidelines recommend its use in patients with active CD as adjunctive therapy or steroid-sparing agent. Although it is generally considered safe in patients with previous cancer, actually there are no studies aimed to evaluate its role and safety in IBD patients with previous malignancy. The only data about patients treated with methtorexate and risk of cancer come from rheumatologic registers. The paper by Buchbinder et al. [13] on 459 patients treated with methotrexate for rheumatoid arthritis (RA) have demonstrated that there is an estimated 50% excess risk of malignancy among methotrexate-exposed RA patients relative to the general population (SIR 1.5, 95% confidence interval [95% CI] 1.2–1.9), with a 3-fold increase in melanoma (SIR 3.0, 95% CI 1.2– 6.2), a 5-fold increase in non-Hodgkin's lymphoma (SIR 5.1, 95% CI 2.2–10.0), and an almost 3-fold increase in lung cancer (SIR 2.9, 95% CI 1.6–4.8) in a 9-years follow up period.
At present, there are no data about safety of MTX in IBD patients with history of cancer.

2. Study Aim

The aims of this study are to evaluate the incidence of new cancer and/or recurrent cancer in CD patients with previous cancer treated with MTX compared with 1) CD patients with previous cancer not treated with MTX and 2) patients without CD and with a previous cancer

3. Definitions

Previous cancers will be defined as those cancers diagnosed **at any time** before the start of MTX therapy. A sub-analysis will be performed for cancers diagnosed **within five years** from the start of MTX therapy. An histological confirmation will be required. If patients had had two cancers, investigators will take into account the most recent cancer.
New cancers are incident cancers that developed in an organ different from the organ associated with the previous cancers or that developed in the same organ but with an indisputably different histological type.
Recurrent cancers are incident cancers that developed either in the same organ of the previous cancer with the same histogical type or in a different organ of the previous cancer but with the same histological type.
Any stage of the cancer will be included in the statistical analysis

4. Study design and statistical analysis

This is a multicenter exploratory prospective cohort study. Incidence rates with their 95% confidence intervals (CI) will be calculated for each group of participants.
Incidence rate ratios (IRR), standardized incidence ratios (SIR), with their 95% CIs, will be calculated as appropriate for the comparisons of incidence rates between the three groups of patients. In addition, Cox regression or Poisson regression models will be used as appropriate.

5. Inclusion criteria

CD patients with previous cancer treated with MTX are defined as:

- Patients with CD and age > 18 years
- Who started MTX treatment from 2005
- With a minimum three-years time clinical follow up from the start of MTX therapy
- Independently from any other treatment and from the duration of MTX therapy
- A subgroup analysis will be performed according to the timing between cancer and MTX starting and according to the MTX duration therapy

CD patients with previous cancer not treated with MTX are defined as:

- Patients with CD and age > 18 years with previous cancer
- Not treated with MTX
- With a minimum three-years clinical follow up from the diagnosis of cancer

Patients without CD and with a previous cancer are defined as:

- Patients from the Lombardia registry of cancer selected with similar age, sex and cancer staging of CD patients with previous cancer treated with MTX
- With a minimum three-years clinical follow up from the diagnosis of cancer

5. Exclusion criteria

Patients ≤ 18 years

6. Bibliography

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